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Jon W Dudas

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for Intellectual Property
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PROVISIONAL PATENT APPLICATION TRANSMITTAL

Attorney Docket No. 22247-10600

Date: August 8, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Provisional Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a request for filing a Provisional Application for Patent under 37 C.F.R. 1.53(c).

1. INVENTOR(S)

Name of first or sole inventor: Dusan MILJKOVIC
Residence: San Diego, CA, United States of America

Name of second joint inventor: Zbigniew PIETRZKOWSKI
Residence: San Diego, CA, United States of America

Name of third joint inventor: Jovan HRANISAVLJEVIC
Residence: Belgrade, Yugoslavia

☐ *Additional inventors are being named on the ____ separately numbered sheet(s) attached hereto.*

2. Title:

COMPOUNDS AND COMPOSITIONS THAT MODULATE METABOLISM, THEIR USE AND RELATED METHODS

3. Enclosed Application Parts

a. 223 pages of specification (including claims)

4. Method of Payment of Fees

☒ Applicant claims small entity status. See 37 C.F.R. 1.27.

☒ A check is enclosed to cover the filing fees. The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 18-1260. A duplicate copy of this document is enclosed.

☐ The calculated fees are to be charged to Deposit Account No. 18-1260. The Commissioner is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to said Deposit Account. A duplicate copy of this document is enclosed.

5. The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

_____

6. Correspondence Address

Attention is directed to the fact that the correspondence address for this application is:

BRADLEY S. MAYHEW
SIDLEY AUSTIN BROWN & WOOD LLP
1501 K STREET, N.W.
WASHINGTON, D.C. 20005

Respectfully,

Bradley S. Mayhew
Reg. No. 50,472

Date August 8, 2003
SIDLEY AUSTIN BROWN & WOOD LLP
1501 K STREET, N.W.
WASHINGTON, D.C. 20005
(202) 736-8752

COMPOUNDS AND COMPOSITIONS THAT MODULATE METABOLISM, THEIR USE AND RELATED METHODS

The present application relates to the following previously filed applications, the entireties of which are herein incorporated by reference: PCT/US01/07527 filed on March 8, 2001; PCT/US02/07199, filed March 8, 2002; and U.S. Provisional Appl. No 60/408,887, filed September 9, 2002.

BACKGROUND OF THE INVENTION

Field of the Invention

The invention relates to compounds and compositions that modulate one or more of various metabolic activities. In particular applications, the invention relates to compounds and compositions that activate AMPK and/or Akt. In particular applications, the invention relates to compounds and compositions having blood glucose lowering activity and/or lipid lowering activity as well as to related methods. In particular applications, the invention relates to an anti-diabetic agent, to an anti-diabetic composition containing the anti-diabetic agent, and to a method for treating diabetes. In other particular applications, the invention relates to methods for screening purine derivatives and/or pyrimidine derivatives to identify compounds having an activity to modulate one or more of various metabolic activities and/or for use as an anti-diabetic agent.

Description of Related Art

Elevated blood glucose and blood lipids are a relatively common underlying condition in numerous metabolic diseases and may be acquired in various ways. Among other causes, elevated blood glucose levels are frequently precipitated by an altered metabolism associated with a diabetic disease state.

The diabetic disease state is characterized by an impaired glucose metabolism that commonly manifests itself in elevated glucose levels in patients suffering therefrom. Generally, diabetes is classified into two distinct subgroups:

(1) Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), which arises when patients lack ß-cells producing insulin in their pancreatic glands, and

(2) Type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), which occurs in patients with, *inter alia*, impaired ß-cell function and/or impaired insulin sensitivity (insulin resistance).

At present, type 2 diabetic patients are primarily treated with hypoglycemic agents such as sulfonylureas that stimulate ß-cell function and/or with agents that enhance tissue sensitivity to insulin. Unfortunately, in many instances such treatment is not completely satisfactory. For example, many patients gradually lose the ability to respond to treatment with sulfonylureas and are thus gradually forced into insulin treatment. Moreover, various adverse effects, including liver toxicity, have been associated with agents prescribed to enhance tissue sensitivity to insulin.

Where existing treatments prove ineffective in normalizing blood sugar levels of patients, there is an increased risk of acquiring diabetic complications. For this reason, discovering and identifying compounds for use in therapeutic approaches to achieve satisfactory glycemic control has become an intensive area of research.

Particularly active areas of investigation have included searches for purine derivatives and pyrimidine derivatives having hypoglycemic activity.

EP 0 224 722 A1, the entirety of which is herein incorporated by reference, discloses methods for making a variety of substituted pyrimidines which have oral hypoglycemic activity and suggests their usefulness in the treatment of type II diabetes and/or obesity with associated insulin resistance.

U.S. Patent 5,057,517, the entirety of which is herein incorporated by reference, discloses a variety of 6-piperazinopurines and heteroaromatic derivatives thereof which have oral hypoglycemic activity and suggests their usefulness in the treatment of type II diabetes and/or obesity with associated insulin resistance. Processes for the preparation of such compounds and compositions containing such compounds as the active ingredient thereof are also disclosed.

EP 1 258 247 A1 and WO 02/092093 A1, the entireties of which are herein incorporated by reference, describe a variety of adenosine derivatives and suggests their usefulness in producing medicines for the treatment of the insulin resistance syndrome and diabetes.

US Patent 6,294,522 and Published US Application 2002/0045595A1, the entireties of which are herein incorporated by reference, disclose a variety of N6 heterocyclic 8 modified adenosine derivatives that are selective, partial or full adenosine A1 receptor partial or full agonists and suggests their usefulness for modifying cardiac activity, modifying adipocyte function, treating central nervous system disorders, and treating diabetic disorders and obesity in mammals, and especially in humans.

WO 01/40246 A1, US Patent 6,258,793 and Published US Application 2002/0037872A1, the entireties of which are herein incorporated by reference, disclose a variety of N6 heterocyclic 5' modified adenosine derivatives that are adenosine A1 receptor partial or full agonists and suggests their usefulness for modifying cardiac activity, modifying adipocyte function, treating central nervous system disorders, and treating diabetic disorders and obesity in mammals, and especially in humans.

EP 1 054 012 A1 and EP 1 300 147 A1, the entireties of which are herein incorporated by reference, disclose A2 receptor antagonists and their pharmacologically acceptable salts or hydrates and suggests their usefulness for preparing medicaments for preventing or treating diabetes mellitus or diabetic complications, and for preparing improving agents for impaired glucose tolerance, potentiating agent for insulin sensitivity or medicaments for preventing or treating obesity.

US Patent 6,525,083, the entirety of which is herein incorporated by reference, discloses methods for making a variety of N-substituted indoles that are agonists or partial agonists of PPAR gamma and suggests their usefulness in the treatment, control or prevention of non-insulin dependent diabetes mellitus (NIDDM), hyperglycemia, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, obesity, vascular restenosis, inflammation, and other PPAR mediated diseases, disorders and conditions.

US Patent 5,547,942, the entirety of which is herein incorporated by reference, discloses treating patients suffering from NIDDM, and their chronic clinical complications which are the result of continuous hyperglycemia, by the administration of adenine nucleotides or adenosine and inorganic phosphate.

Inosine and uridine at concentrations of 10^{-5} M have been shown to increase glucose uptake in rabbit hearts (Hait et al., Circulation, 1972, 46(2):333-46, the entirety of which is herein incorporated by reference) and rat diaphragm (Kypson et al., J. Pharmacol. and Exptl. Therapeutics, 1976, 199(3):565-574, the entirety of which is herein incorporated by reference).

US Patent 5,190,948, the entirety of which is herein incorporated by reference, discloses methods comprising administering uridine to diabetic patients for treating certain peripheral complications of diabetes, including neuropathy, retinopathy and peripheral vascularpathy.

US Patent 6,316,426 and Published US Application 2002/0035086A1, the entireties of which are herein incorporated by reference, disclose compositions comprising acyl derivatives of cytidine and uridine and their use in treating hepatopathies, diabetes, heart disease, cerebrovascular disorders, Parkinson's disease, infant respiratory distress syndrome and for enhancement of phospholipid biosynthesis comprising administering the acyl derivatives of the invention to an animal.

Another area of active research in the field of diabetes relates to the potential role of AMP-activated protein kinase (AMPK) in the treatment of the disease. Recent data collected in several laboratories indicate that AMPK plays a key role in regulation of carbohydrate and fat metabolism, serving as "a metabolic master switch" in response to alterations in cellular energy charge. (Winder et al, Am J Physiol, 2777: E1-10, 1999, the entirety of which is herein incorporated by reference; Winder, J Appl Physiol, 91:1017-1028, 2001, the entirety of which is herein incorporated by reference). AMPK is known to effect increases in glucose uptake and increases in fatty acid oxidation in skeletal muscle,

increases in fatty acid oxidation, decreases in cholesterol synthesis, and decreases in lipogenesis in the liver. Furthermore, AMPK is known to modulate insulin secretion in pancreatic islets. AMPK phosphorylates numerous target proteins, and the resulting phosphorylation, in turn, may increase or decrease the rate of the metabolic pathway in which the protein target plays a regulatory role. One form of AMPK is expressed in the cell nucleus, and recent evidence suggests that AMPK can also influence metabolism by regulating gene expression.

It has also recently been reported that methods to increase intracellular levels of activated AMPK result in one of a number of beneficial effects, including reducing insulin resistance and glucose concentrations in an organism. For example, WO 01/66146 A1, the entirety of which is herein incorporated by reference, discloses certain plant extract fractions that have potent hypoglycemic and/or lipid lowering activity, and U.S. Provisional Patent Application 60/408,887 and WO 02/072148 A1, the entireties of which are herein incorporated by reference, further disclose that the extracts have the property to activate adenosine 5'-monophosphate-activated protein kinase (AMPK). WO 01/93874 A1, the entirety of which is herein incorporated by reference, discloses administering an AMP-activated protein kinase (AMPK) activator to reduce insulin resistance in a mammal suffering from obesity, type 2 diabetes, or muscle paralysis. Moreover, WO 02/09726 A1, the entirety of which is herein incorporated by reference, discloses that long-term usage of AICAR (5-amino, 4-imidazole carboxamide riboside), a known activator of AMPK, produces sustained metabolic and biological changes in mammals that reduce insulin resistance and suggest the usefulness of such a treatment in patients suffering from diseases

and conditions such as diabetes, hypertension, atherosclerosis, polycystic ovary syndrome and gallstones.

Recent data additionally indicate that activated Akt, a serine/threonine kinase also known in the art as protein kinase B (PKB) or RAC-PK, may contribute to the insulin-sensitizing effects of thiazolidinediones (TZDs) in human skeletal muscle (Meyer et al., Diabetes. 2002 Sep;51(9):2691-7, the entirety of which is herein incorporated by reference). Akt is believed to be activated by insulin-induced cascade and to be involved in stimulation of glucose uptake through GLUT-4. Moreover, Akt-deficient animals (knockout) have been reported to be severely diabetic and insulin resistant (Cho et al., Science, 292, 1728-1731, 2001, the entirety of which is herein incorporated by reference). In addition, protein TRB3, which is believed to be a negative regulator of Akt, has been proposed as molecular target for development of new anti-diabetic drugs and to improve functioning of Akt (Mintminy et al, Science, 300, 1574-77, 2003, the entirety of which is herein incorporated by reference).

Although many methods and compositions are known for modulating various metabolic activities associated with elevated blood glucose and/or blood lipids, all or almost all of the known methods and compositions suffer from one or more disadvantages. Therefore, a need remains for improved compositions and methods for modulating various metabolic activities associated with elevated blood glucose and/or blood lipids.

SUMMARY OF THE INVENTION

According to the invention, compounds including various purine derivatives and pyrimidine derivatives have been found to be potent activators of adenosine 5'-monophosphate-activated protein kinase (AMPK) and/or Akt. Thus, an aspect of the invention relates to purine derivatives, including cytokinins, adenine derivatives, and guanine derivatives, as well as to pyrimidine derivatives, including cytosine derivatives, that are activators of AMPK and/or Akt. In one aspect, the present invention concerns the use of such activators, as well as compositions comprising such activators, to increase intracellular levels of activated AMPK and/or activated Akt to result in one of a number of beneficial effects in an organism. An aspect of the present invention also concerns the use of such activators, as well as compositions comprising such activators, in the prevention or treatment of diseases and conditions treatable through increasing intracellular levels of activated AMPK and/or activated Akt, such as diseases and conditions associated with elevated blood glucose and/or blood lipids, for example. An aspect of the present invention is particularly concerned with the treatment of insulin resistance and/or type II diabetes. The invention provides, among other aspects, an anti-diabetic agent, an anti-diabetic composition containing the anti-diabetic agent, a foodstuff or beverage containing the anti-diabetic agent, kits based on the anti-diabetic agent, a method for preventing or treating diabetes or impaired glucose tolerance, and a method of decreasing blood glucose level. The invention additionally provides screening methods comprising measuring the ability of a purine derivative, such as a cytokinin, an adenine derivative, or a guanine derivative, and/or measuring the ability of a pyrimidine derivative, such as a cytosine derivative, to increase

intracellular levels of activated AMPK and/or activated Akt. The invention additionally provides screening methods comprising measuring the ability of a purine derivative, such as a cytokinin, an adenine derivative, or a guanine derivative, and/or measuring the ability of a pyrimidine derivative, such as a cytosine derivative, to increase expression and/or function of the glucose transporter GLUT-4.

Various objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of preferred embodiments of the contemplated invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

An advantageous aspect of the instant invention concerns the discovery that, when administered in a therapeutically effective dose, compounds and compositions of the invention modulate one or more of various metabolic activities. In particularly preferred embodiments of the contemplated invention, when administered in a therapeutically effective dose, compounds and compositions of the invention will reduce blood glucose concentrations in an organism suffering from an elevated glucose concentration. While not wishing to be bound by theory, applicants believe a mechanism involving the activation of AMPK and/or Akt underlies the reduction in blood glucose that follows administering a contemplated compound, or a composition comprising a contemplated compound, to an organism. As such, the utility of the inventive subject matter additionally extends to methods for treating a variety of disorders that are ameliorated through activation of AMPK and/or Akt, such as those disorders well known in the art and/or exemplified in the instant application.

A. Terms

The term "alkyl" refers to the radical of aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In preferred embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1 -C_{30} for straight chain, C_3 -C_{30} for branched chain), and more preferably 20 or fewer. A preferred embodiment of an alkyl is a (C_1-C_{25})alkyl. Another preferred embodiment of an alkyl is a (C_1-C_{20})alkyl. Another preferred embodiment of an alkyl is a (C_1-C_{15})alkyl. In preferred embodiments, cycloalkyls have from 4-10 carbon atoms in their ring structure, and more preferably have 5, 6 or 7 carbons in their ring structure.

Moreover, the term "alkyl" as used throughout the specification and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having one or more substituents on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, aryl, alkenyl, alkynyl, arylcarbonyloxy, alkoxy alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acyl, heteroacyl, acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, alkylsilyl, alkylseleno, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aralkyl, or an aromatic or

heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. Cycloalkyls can be further substituted, e.g., with the substituents described above. Preferred embodiments of alkyl groups include those having an aliphatic backbone containing one or more heteroatoms. Other preferred embodiments of alkyl groups include those having an aliphatic backbone that does not contain a heteroatom. An "aralkyl" moiety is an alkyl substituted with an aryl (e.g., phenylmethyl (benzyl)). Thus, the term alkyl as used herein, unless otherwise noted, is also meant to include such aralkyl moieties. The term alkyl as used herein further encompasses heteroalkyls, as defined below.

Unless the number of carbons is otherwise specified, "lower alkyl" as used herein refers to an alkyl group having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure. Lower alkyls are among espacially preferred alkyl groups. A preferred embodiment of a lower alkyl is a $(C_1\text{-}C_{10})$alkyl. Another preferred embodiment is a $(C_1\text{-}C_8)$alkyl. Another preferred embodiment is a $(C_1\text{-}C_6)$alkyl. And an especially preferred alkyl is a $(C_1\text{-}C_4)$alkyl.

The terms "alkenyl" and "alkynyl" as used herein refer to unsaturated aliphatic groups analogous to alkyls as defined above, where alkenyls and alkynyls differ from alkyls in that alkenyls and alkynyls contain at least one double or triple bond, respectively. Examples of alkenyl residues include, for example, isobutenyl, isopentenyl, vinyl, 1-propenyl, 2-propenyl (=allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl, and 1,3-pentadienyl. Examples of alkynyl residues include ethynyl, 1-propynyl, 2-propynyl (=propargyl), and 2-butynyl. In a preferred embodiment, a compound comprises

the radical of an unsaturated aliphatic group as an alkyl substituent. For example, an isopentenyl residue could equally be considered methyl residue substituted with isobutenyl.

The term "heteroalkyl" as used herein refers to those alkyls having an aliphatic backbone containing one or more heteroatoms. Examples of heteroalkyl residues include, for example, methoxymethyl, 3-thiomethylpropyl, and 2-thiomethoxyethoxymethyl and the like. Up to two heteroatoms may be consecutive, such as $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$, for example. In a preferred embodiment, a heteroalkyl includes up to four heteroatoms. In other preferred embodiments, a heteroalkyl contains one, two or three heteroatoms. In a preferred embodiment, the heteroatom is selected from O, N, S and Si. In another preferred embodiment, the heteroatom is selected from P, B and Se. In a preferred embodiment, the heteroatom is O. In a preferred embodiment, the heteroatom is N. In a preferred embodiment, the heteroatom is S. In a preferred embodiment, the heteroatom is Si. A preferred embodiment of an alkyl is a heteroalkyl containing 1 to 29 aliphatic carbon atoms. Another preferred embodiment is a heteroalkyl containing 1 to 19 aliphatic carbon atoms. A preferred embodiment is a heteroalkyl containing 1 to 9 aliphatic carbon atoms. Another preferred embodiment is a heteroalkyl containing 1 to 7 aliphatic carbon atoms. Another preferred embodiment is a heteroalkyl containing 1 to 5 aliphatic carbon atoms. Another preferred of an alkyl is a heteroalkyl containing 1 to 3 aliphatic carbon atoms. And an especially preferred alkyl is a heteroalkyl containing 1 to 2 aliphatic carbon atoms. Likewise, the term "heteroalkenyl" as used herein refers to those alkenyls having an aliphatic backbone containing one or more heteroatoms, and the term "heteroalkynyl" as used herein refers to those alkynyls having an aliphatic backbone containing one or more heteroatoms.

The term "aryl" as used herein includes 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl groups also include polycyclic fused aromatic groups such as naphthyl, quinolyl, indolyl, and the like. The term aryl as used herein encompasses those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaryls" or "heteroaromatics". The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, aralkyl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 10-membered ring structures, more preferably 4- to 7-membered rings, which ring structures include one to four heteroatoms. Heterocyclyl groups include pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, lactones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for

example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, aralkyl, or an aromatic or heteroaromatic moiety.

The terms "polycyclyl" or "polycyclic group" refer to two or more cyclic rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, aralkyl, or an aromatic or heteroaromatic moiety.

The term "acyl" refers to a moiety of the formula --C(O)R', wherein R' encompasses, for example, hydrogen or an alkyl, aryl, aralkyl or heterocyclyl group. In

preferred embodiments, R' of the acyl group is alkyl, aryl, alkaryl, aralkyl, amino acid residue, heteroaromatic, alkoxyalkyl including methoxymethyl; arylalkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with halogen, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy, or the residue of an amino acid. Acyl substituents may be derived from carboxylic acids which include, but are not limited to, compounds selected from the group consisting of a fatty acid, an amino acid, acetic acid, nicotinic acid, dicarboxylic acids, tricarboxylic acids, citric acid, lactic acid, p-aminobenzoic acid and orotic acid. In preferred embodiments acyl substituents may be derived from carboxylic acids in which the atom adjacent to the carbonyl carbon atom is another carbon atom. In preferred embodiments acyl substituents may be derived from carboxylic acids in which the atom adjacent to the carbonyl carbon atom is an oxygen that is furthermore covalently linked to another carbon atom. In a preferred embodiment, the acyl substituents are substantially nontoxic carboxylic acids. Especially advantageous acyl substituents are carboxylic acids which are normally present in the body, either as dietary constituents or as intermediary metabolites.

The term "heteroacyl" as used herein refers to a moiety of the formula --X(O)R' or --X(OH)R', wherein X is a heteroatom and R' encompasses, for example, hydrogen or an alkyl, aryl, aralkyl or heterocyclyl groups. In a preferred embodiment, the X is selected from N, S, P, Si, B or Se. In another preferred embodiment, X is selected from N, S, P and Si. In a more preferred embodiment, the X is selected from N, S and P. In a more preferred embodiment, the "heteroacyl" is a moiety of the formula --X(O)R', and X is selected from N and S. In a preferred embodiment, X is S. In another preferred embodiment, X is N.

The term "acyl derivative" as used herein means any derivative of a compound in which one or more acyl groups are present. Examples of acyl derivatives are those wherein the hydrogen atom in an --OH group, and/or one or both of the hydrogen atoms in the $--NH_2$ group, are replaced by an acyl group of --C(O)R', wherein R' may be, as non-limiting examples, hydrogen or an alkyl, aryl, aralkyl, or heterocyclyl group. Likewise, the term "heteroacyl derivative" as used herein refers to any derivative of a compound in which one or more heteroacyl groups are present.

The term "hydrocarbylcarbonyl" as used herein means an acyl radical of a carboxylic acid in which the atom adjacent to the carbonyl carbon atom is another carbon atom. The parent carboxylic acid may, for example, be a fatty acid, an aromatic acid (e.g. benzoate, nicotinoate, or their congeners), an amino acid, a cycloalkylcarboxylic acid, or a dicarboxylic acid.

The term "hydrocarbyloxycarbonyl" as used herein means an acyl radical of a carboxylic acid in which the atom adjacent to the carbonyl carbon atom is oxygen which is furthermore covalently linked to another carbon atom. This can also be described as a radical of a carbonate ester of an alcohol, which, when cleaved from a purine or pyrimidine following administration, degrades further into carbon dioxide and an alcohol. Advantageous alcohols are those which are of low toxicity, particularly those which enter readily into normal metabolic or eliminative pathways.

The term "fatty acids" as used herein means aliphatic carboxylic acids having at least 2 carbon atoms. In one embodiment, such fatty acids have no more than 22 carbon atoms. Such fatty acids may be saturated, partially saturated or polyunsaturated.

The term "amino acids" as used herein encompasses, but is not limited to, glycine, the L or R forms of alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, proline, hydroxyproline, serine, threonine, cysteine, cystine, methionine, tryptophan, aspartic acid, glutamic acid, arginine, lysine, histidine, ornithine, hydroxylysine, carnitine, and other naturally occurring amino acids. The L form of these amino acids is an especially preferred embodiment.

The term "dicarboxylic acids" as used herein means fatty acids with a second carboxylic acid substituent.

The term "halogen" is meant to include fluorine, chlorine, bromine and iodine, or fluoro, chloro, bromo, and iodo.

The term "saccharide" is meant to include both aldoses (sugars derived from monosaccharides having an empirical formula $(CH_2O)_n$ where n equals 3 or some larger number and the monosaccharide has an aldehyde or like group at the end of its chain) and ketoses (derivatives of monosaccharides having a ketone group within its structure other than at its end). Saccharides also include both the ring and open chain forms and the levorotatory (L) and the dextrorotatory (D) forms and the alpha and the beta forms thereof. Both substituted and unsubstituted saccharides are encompassed by the term. Preferred substituted saccharides include acyl derivatives.

Examples of saccharides are pentoses, which include ribose, arabinose, xylose, lyxose, ribulose, and xylulose. Preferred pentoses are the pentoses ribose and 2'-deoxyribose in which the hydroxide group and the 2'-position is replaced by hydrogen. The beta-D forms are also particularly preferred. Other useful saccharides include hexoses such as allose, altrose, glucose, mannose, gluose, idose, galactose, talose, psicose, fructose,

sorbose, and tagatose. Tetroses include erythrose, threose, and erythrulose. Thus, when in this document reference is made to a chemical whose name includes "saccharide", or elsewhere where the word saccharide is used it should be understood that the alpha or beta, D or L, and oxy or deoxy forms of saccharides are contemplated. Furthermore, in preferred embodiments according to the present invention, the term "saccharide" in a name, or the term saccharide in text both refers to ribose or 2'-deoxyribose. The term 5'phospho-ribosyl will be understood to encompass 5' mono-, di-, and tri-phospho-ribosyl; and the term 5'phospho-deoxyribosyl will be understood to encompass 5' mono-, di-, and tri-phospho-deoxyribosyl.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

The term "substantially pure" as used herein, refers to a composition which is substantially free of impurities, including (but not limited to) starting materials, side products, undesired co-eluting compounds or any other undesired component. A composition is "substantially pure" when impurities comprise less than about 25% of the composition by weight. In a preferred embodiment, a composition is substantially pure when impurities comprise less than about 20% of the composition by weight. In a more preferred embodiment, a composition is substantially pure when impurities comprise less than about 15% of the composition by weight. In a still more preferred embodiment, a composition is substantially pure when impurities comprise less than about 10% of the composition by weight. In a still more preferred embodiment, a composition is substantially pure when impurities comprise less than about 5% of the composition by weight. In an

especially preferred embodiment, a composition is substantially pure when impurities comprise less than about 1% of the composition by weight.

The term "pharmaceutical composition" refers to a composition comprising as active ingredient(s) one or more contemplated compounds of the invention, such as a purine derivative or a pyrimidine derivative, or a pharmaceutically acceptable salt, racemate, enantiomer, tautomer, solvate, hydrate, pro-drug and/or polymorph thereof, and may also optionally contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The compositions may be presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy. Dosage regimes may be adjusted for the purpose to improving the therapeutic response. For example, several divided dosages may be administered daily or the dose may be proportionally reduced over time. A person skilled in the art normally may determine the effective dosage amount and the appropriate regime.

The term "substantially pure pharmaceutical composition" refers to a pharmaceutical composition as defined above, where the one or more contemplated compounds of the invention, the optional pharmaceutically acceptable carrier, and the optional other therapeutic ingredients comprise, in total, at least about 75% of the composition by weight. In a preferred embodiment of a substantially pure pharmaceutical composition, one or more contemplated compounds of the invention, the optional pharmaceutically acceptable carrier, and the optional other therapeutic ingredients comprise, in total, at least about 85% of the composition by weight. In a more preferred embodiment of a substantially pure pharmaceutical composition, one or more contemplated compounds of the invention, the optional pharmaceutically acceptable carrier, and the optional other therapeutic ingredients comprise, in total, at least about 90% of the composition by weight. In a still more preferred

embodiment of a substantially pure pharmaceutical composition, one or more contemplated compounds of the invention, the optional pharmaceutically acceptable carrier, and the optional other therapeutic ingredients comprise, in total, at least about 95% of the composition by weight. In an especially preferred embodiment of a substantially pure pharmaceutical composition, one or more contemplated compounds of the invention, the optional pharmaceutically acceptable carrier, and the optional other therapeutic ingredients comprise, in total, at least about 99% of the composition by weight.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The term "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutical carriers, diluents, buffers, excipients, solid fillers, and the like, including (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar–agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) coloring agents: (11)

phosphate-buffered saline solution (12) emulsions, such as an oil/water or water/oil emulsion; (12) adjuvants; and (13) sterile aqueous solutions, for example. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some additional examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. Additional suitable pharmaceutical carriers and their formulations are described in REMINGTON'S PHARMACEUTICAL SCIENCES (Mack Publishing Co., Easton, 19th ed. 1995, the entirety of which is herein incorporate by reference) as well as in US Patent 6,416,965, the entirety of which is herein incorporated by reference). As one of skill in the art would recognize, a "carrier" that comprises substantial amounts of unknown compounds and/or impurities is not preferred for pharmaceutical use. Thus, preferred pharmaceutically acceptable carriers are, therefore, those in which such unknown compounds and/or impurities comprise, in total, less than about 25% of the carrier by weight. More preferred

pharmaceutically acceptable carriers are those in which such unknown compounds and/or impurities comprise, in total, less than about 20% of the carrier by weight. Still more preferred pharmaceutically acceptable carriers are those in which such unknown compounds and/or impurities comprise, in total, less than about 20% of the carrier by weight. Still more preferred pharmaceutically acceptable carriers are those in which such unknown compounds and/or impurities comprise, in total, less than about 15% of the carrier by weight. Still more preferred pharmaceutically acceptable carriers are those in which such unknown compounds and/or impurities comprise, in total, less than about 10% of the carrier by weight. Still more preferred pharmaceutically acceptable carriers are those in which such unknown compounds and/or impurities comprise, in total, less than about 5% of the carrier by weight. Especially preferred pharmaceutically acceptable carriers are those in which such unknown compounds and/or impurities comprise, in total, less than about 1% of the carrier by weight.

The term "pharmaceutically acceptable salt" is intended to encompass all acceptable salts that can be used for modifying the solubility or hydrolysis characteristics or can be used in sustained release or pro-drug formulations. Certain embodiments of the present compounds may contain a basic functional group, such as amino or alkylamino, and are, thus, capable of forming pharmaceutically acceptable salts with pharmaceutically-acceptable acids. Thus, the term "pharmaceutically acceptable salts" encompasses the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus

formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, e.g., Berge et al. (1977) "Pharmaceutical Salts", J. Pharm. Sci. 66:1-19) In other cases, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically-acceptable salts with pharmaceutically-acceptable bases. Thus, the term "pharmaceutically acceptable salts" encompasses the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal action, with ammonia, or with a pharmaceutically-acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. (See, for example, Berge et al., supra) As one of skill in the art would recognize, where a compound is a salt, reference to "a salt thereof" denotes alternative acceptable salts of the compound, including pharmaceutically acceptable salts of the compound. For example, reference to the salt of N6 – benzyladenine hydrochloride denotes salts of N6 – benzyladenine comprising an acceptable alternative to the hydrochloride salt. Similarly, where a given compound is a

pharmaceutically acceptable salt, reference to "a pharmaceutically acceptable salt thereof" denotes alternative pharmaceutically acceptable salts of the given compound.

The term "pro-drug" as used herein refers to a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide a contemplated compound of the invention. A prefered embodiment of a pro-drug is a compoud that can hydrolyze, oxidize, or otherwise react under biological conditions to result in a cytokinin of structure (I), an adenine derivative of structure (II), a guanine derivative of structure (III), or a cytosine derivative of structure (IV). For example, carboxylic esters are conveniently formed by esterifying carboxylic acid functionalities; if the contemplated compound includes an acid functional group it can be esterified to provide a pro-drug. Various pro-drugs are well known in the art (For examples of pro-drugs, see: Design of Prodrugs, edited by H. Bundgaard, Elsevier, 1985; Methods in Enzymology, vol. 42, p. 309-396, edited by K. Widder et al., Academic Press, 1985; A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H, Bundgaard, chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, p. 113-191, 1991; H. Bundgaard, Advanced Drug Delivery Reviews," 8, 1-38, 1992; H. Bundgaard et al., Journal of Pharmaceutical Sciences, 77, 285, 1988; and N. Kakeya et al., Chem. Phar. Bull., 32, 692, 1984).

The term "therapeutically effective amount" as used herein refers to an amount that provides therapeutic effects for a given condition and administration regime. The amount will vary with the condition being treated, the stage of advancement of the condition, and the type and concentration of formulation applied. Appropriate amounts in any given instance

will be readily apparent to those skilled in the art or capable of determination by routine experimentation.

The term "patient" as used herein refers to a mammal which is being treated prophylactically and/or for a condition having visible and/or otherwise measurable symptoms. Preferably the patient is a human. In a preferred embodiment, the patient is a patient receiving treatment under the direction of a healthcare professional. Preferred embodiments also include patients receiving self-directed treatment.

The term "coadministered" as used herein means that at least two of the compounds of the invention are administered during a time frame wherein the respective periods of pharmacological activity overlap. In a preferred embodiment, a compound is administered at a time when the pharmacological activity of a previously administered compound is at least half-maximal. In another preferred embodiment, when at least two compounds of the invention are administered, the duration of time between adminstering the first and second compounds does not exceed the half-life ($t_{1/2}$) of the first administered compound.

The term "unit dosage" as used herein refers to a physically discrete unit, suitable for oral or parenteral administration, containing an individual quantity of the active component in association with a pharmaceutically acceptable carrier or diluent, the quantity of the active component being such that at least one unit or severable fraction of a unit is required for a single therapeutic administration. In the case of severable units, such as scored tablets, at least one severable fraction such as one-half or one-quarter of the unit may be all that is required for a single therapeutic administration. It will be appreciated that the term "unit dosage" does not include mere powders or solutions except when the powders or solutions have been prepared so as to be suitable for oral administration, e.g., in capsules, cachets,

pills, tablets, lozenges or other measured forms suitable for oral ingestion, or have been prepared so as to be suitable for parenteral administration, e.g., in vials of a solution suitable for parenteral injection. The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents, in either single or multiple doses. Pharmaceutical compositions are preferably administered in unit dosage form.

The terms "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

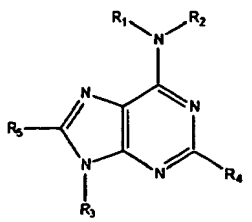
The terms "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

The term "tissue" is intended to include intact cells, blood, blood preparations such as plasma and serum, bones, joints, muscles, smooth muscles, and organs, both *in vivo* and *in vitro*.

As used herein, the term "AICAR" refers to 5'-aminoimidazole 4-carboxamide 1-ribonucleotide.

The term "cytokinin" is well known to those of skill in the art. For example, various cytokinin compounds have been described in the following articles, the entirety of each of which is herein incorporated by reference: "Cytokinins", Annual Review of Plant Physiology, Vol. 21, 1970, pages 359-383, authored by Skoog and Armstrong; in the article entitled "Cytokinins: Syntheses, Mass Spectra and Biological Activity of Compounds Related to Zeatin", Proceedings of the National Academy of Science, Vol. 63, No. 1, 1969, pages 175-185, by Leonard, Hecht, Skoog and Schmitz; in the article entitled "Cytokinins Influence of Side-Chain Planarity of N6-Substituted Adenines and Adenosines On Their Activity in Promoting Cell Growth", Phytochemistry, Vol. 9, 1970, pages 1907-1913, by Hecht, Leonard, Schmitz and Skoog; and in the article entitled "Cytokinins: Structure/Activity Relationships", Phytochemistry, Vol. 6, 1967, pages 1169-1192, by Skoog, Hamzi, Szweykowska et al. See also Letham (pp. 205-264 in Phytohormones and Related Compounds, Vol. I, D. S. Letham et al, eds., 1978), Chen (Physiologia Plantarum Vol. 101, 1997, pages 665-673) and US Patent 4,581,056, the entirety of each of which is herein incorporated by reference.

As used herein, the term "cytokinin" is a generic name encompassing naturally occurring and synthetic chemical substances that can generally be classified as purine derivatives having the following structure:



wherein:

- R_1 is H;
- R_2 is alkyl, lower alkyl or alkenyl, preferably (C_1-C_{10})alkyl or (C_2-C_{10})alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl or alkenyl.

Moreover, the term "cytokinin" is herein defined to further encompass racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs and/or salts, including pharmaceutically acceptable salts, of a cytokinin as defined by the structure immediately above. In a preferred embodiment, cytokinins are naturally occurring. Preferred embodiments of cytokinins include racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs and/or salts (including alternative salts, as well as pharmaceutically acceptable salts, and alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of those cytokinins that are naturally occurring. In a preferred embodiment, cytokinins are synthetic chemical substances that are non-naturally occurring. Preferred embodiments of cytokinins include racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs and/or salts (including alternative salts, as well as pharmaceutically acceptable salts, and alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of those cytokinins that are non-naturally occurring. Moreover, the term "cytokinin" is herein expressly defined to encompass each of

the following compounds, as well as racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs, salts (including alternative salts, as well as pharmaceutically acceptable salts, including alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives thereof: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; dihydrozeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside.

As used herein, the term "AMPK" refers to adenosine 5'-monophosphate-activated protein kinase, an enzyme well known in the art (See, for example, Fryer et al, Biochem J. 2002 Apr 1;363(Pt 1):167-74, the entirety of which is herein incorporated by reference).

As used herein the term "compound that activates AMPK" refers to any compound that, when placed in contact with an appropriate cell or organism, increases phosphorylation of AMPK and/or increases phosphorylation by AMPK of any one of its numerous protein targets. (Winder et al, Am J Physiol, 2777: E1-10, 1999, the entirety of which is herein incorporated by reference) The term is not limited by the mechanism underlying how the phosphorylation of AMPK and/or phosphorylation by AMPK is increased. The potential mechanisms through which such a compound may act include, but are not limited to, allosteric mechanisms that affect, directly or indirectly, AMPK activity, as well as mechanisms that act, directly or indirectly, to promote activation of AMPK catalytic activity through phosphorylation of AMPK catalyzed by a distinct upstream kinase, such as by AMPK kinase (AMPKK). Among other potential mechanisms, such a compound may prevent or reduce the inhibition of AMPK activity exerted through proteins that otherwise inhibit the activity of AMPK.

As used herein, the term "Akt" refers to a serine/threonine kinase that is also known in the art as protein kinase B (PKB) or RAC-PK (See, for example, Brazil and Hemmings, Trends Biochem Sci 2001 Nov;26(11):657-64, the entirety of which is herein incorporated by reference).

As used herein the term "compound that activates Akt" refers to any compound that, when placed in contact with an appropriate cell or organism, increases phosphorylation of Akt and/or increases phosphorylation by Akt of any one of its numerous protein targets.

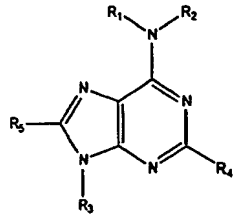
The term is not limited by the mechanism underlying how the phosphorylation of Akt and/or phosphorylation by Akt is increased. The potential mechanisms through which such a compound may act include, but are not limited to, allosteric mechanisms that affect, directly or indirectly, Akt activity, as well as mechanisms that act, directly or indirectly, to promote activation of Akt catalytic activity through phosphorylation of Akt catalyzed by a distinct upstream kinase. Among other potential mechanisms, such a compound may prevent or reduce the inhibition of Akt activity exerted through proteins that otherwise inhibit the activity of Akt.

As used herein, the term "elevated glucose concentration" refers to a concentration that is above the clinical range considered normal (*i.e.*, in humans, above a fasting glucose concentration of about 110 mg/dl). Similarly, the term "elevated lipid concentration" refers to a concentration of blood lipids that is above the clinical range considered normal.

B. Compounds of the Invention

Cytokinins

Contemplated compounds of the invention include cytokinins having the following structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

Particularly preferred cytokinins include those compounds of the aforementioned structure (I) and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, wherein:

- R_1 is hydrogen or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl (preferably $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{20})$alkyl, $(C_1\text{-}C_{15})$alkyl, $(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_8)$alkyl, $(C_1\text{-}C_7)$alkyl), $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_4)$alkyl or heteroalkyl) or alkenyl (preferably $(C_2\text{-}C_{30})$alkenyl, $(C_2\text{-}C_{20})$alkenyl, $(C_2\text{-}C_{15})$alkenyl, $(C_1\text{-}C_{10})$alkenyl, $(C_2\text{-}C_7)$alkenyl), $(C_2\text{-}C_5)$alkenyl), $(C_2\text{-}C_4)$alkenyl) or heteroalkenyl), either unsubstituted or substituted with one or more of: hydroxy; halogen (preferably chloro, fluoro and/or bromo); alkyl (preferably $(C_1\text{-}C_7)$alkyl or heteroalkyl); alkenyl (preferably $(C_2\text{-}C_7)$alkenyl or heteroalkenyl); alkynyl (preferably $(C_2\text{-}C_7)$alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl); alkaryl; aralkyl;

cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);

- R_3 is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl (preferably $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{20})$alkyl, $(C_1\text{-}C_{15})$alkyl, $(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_7)$alkyl) or heteroalkyl) or alkenyl (preferably $(C_1\text{-}C_{30})$alkenyl, $(C_1\text{-}C_{20})$alkenyl, $(C_1\text{-}C_{15})$alkenyl, $(C_1\text{-}C_{10})$alkenyl, $(C_1\text{-}C_7)$alkenyl) or heteroalkenyl).

Particularly preferred cytokinins include those compounds of the aforementioned structure (I) and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, wherein:

- R_1 is hydrogen or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkenyl (preferably $(C_2\text{-}C_{10})$alkenyl or $(C_2\text{-}C_7)$alkenyl or heteralkenyl), either unsubstituted or substituted with one or more: hydroxy; halogen (preferably chloro, fluoro and/or bromo); alkyl (preferably $(C_1\text{-}C_7)$alkyl or heteroalkyl); alkenyl (preferably $(C_2\text{-}C_7)$alkenyl or heteroalkenyl); alkynyl (preferably $(C_2\text{-}C_7)$alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl); alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl and/or cycloheptyl); cycloalkenyl

(preferably cyclopropenyl, cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);

- R_3 is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl (preferably $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{20})$alkyl, $(C_1\text{-}C_{15})$alkyl, $(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_7)$alkyl) or heteroalkyl) or alkenyl (preferably $(C_1\text{-}C_{30})$alkenyl, $(C_1\text{-}C_{20})$alkenyl, $(C_1\text{-}C_{15})$alkenyl, $(C_1\text{-}C_{10})$alkenyl, $(C_1\text{-}C_7)$alkenyl) or heteroalkyl).

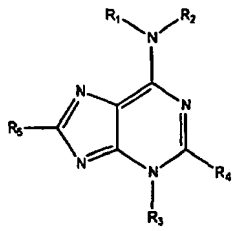
Particularly preferred embodiments of the aforementioned structure (I) include those cytokinins having R_1, R_2, R_3, R_4 and R_5 as defined in Table 1:

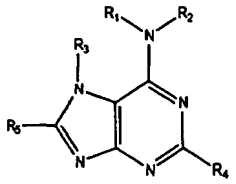
Table 1 – Preferred Cytokinins

Structure	R_1	R_2	R_3	R_4	R_5
(I-a)	H	Isopentenyl	H	H	H
(I-b)	H	Furfuryl	H	H	H
(I-c)	H	Benzyl	Glucosyl	H	H
(I-d)	H	Benzyl	H	H	H
(I-e)	H	Isopentenyl	Ribosyl	H	H
(I-f)	H	Isopentenyl	Glucosyl	H	H
(I-g)	H	Isopentenyl	Glucosyl	Methylthio	H
(I-h)	H	Isopentenyl	5'-phospo-ribosyl	H	Methylthio
(I-i)	H	Benzyl	Ribosyl	H	H
(I-j)	H	Benzyl	5'-phospo-ribosyl	Methyl	H
(I-k)	H	Benzyl	Ribosyl	Methylthio	H
(I-l)	H	Isopentenyl	H	Methylthio	H
(I-m)	H	Furfuryl	Ribosyl	H	H
(I-n)	H	Benzyl	5'-phospo-ribosyl	H	Methyl

Contemplated cytokinins further encompass racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts (including pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of a cytokinin as defined by the above

structure (I). Particularly prefered tautomers of structure (I) are those cytokinins having the following structures:





and/or a racemate, enantiomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein R_1, R_2, R_3, R_4 and R_5 are as defined in any above embodiment of a cytokin having aforementioned structure (I) and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

In a preferred embodiment of the contemplated invention, contemplated cytokinins are naturally occurring. In a preferred embodiment of the contemplated invention, cytokinins are hydrates, solvates, tautomers, salts (including alternative salts, as well as pharmaceutically acceptable salts, and alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of those cytokinins that are naturally occurring. In a preferred embodiment of the contemplated invention, cytokinins are synthetic chemical substances that are non-naturally occurring. In a preferred embodiment of the contemplated invention, cytokinins are hydrates, solvates, tautomers, salts (including alternative salts, as well as pharmaceutically acceptable salts, and alternative pharmaceutically acceptable salts),

acyl derivatives and/or heteroacyl derivatives of such cytokinins that are non-naturally occurring synthetic chemical substances. Contemplated cytokinins further encompass each of the following compounds, as well as enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs, salts (or alternative salts where the cytokinin is a salt), acyl derivatives and/or heteroacyl derivatives thereof: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; dihydrozeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside.

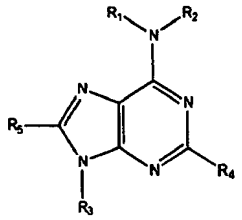
Preferred embodiments of contemplated cytokinins include N6-gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside. Preferred embodiments of contemplated cytokinins further include acyl derivatives of one or more of N6-gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside. Particularly preferred embodiments of contemplated cytokinins further include mono-acyl derivatives of one or more of N6-gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside. Preferred embodiments of contemplated cytokinins further include heteroacyl derivatives of one or more of N6-gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside. Other preferred embodiments of contemplated cytokinins include mono-heteroacyl derivatives of one or more of N6-gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside.

Additional preferred embodiments of the contemplated invention include racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs, salts (including alternative salts, as well as pharmaceutically acceptable salts, including alternative

pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of any of the aforementioned cytokinins described in this subsection ("Cytokinins").

Adenine Derivatives

Contemplated compounds of the invention include derivatives of adenine defined by the following structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Preferred derivatives of adenine include those compounds of the aforementioned formula (II) wherein:

- R_1 and R_2 are the same or different and are hydrogen or alkyl (preferably (C_1-C_{10})alkyl or (C_1-C_7)alkyl or heteroalkyl), either unsubstituted or substituted with one or more hydroxy; halogen (preferably chloro, fluoro and/or bromo); alkyl (preferably (C_1-C_7)alkyl or heteroalkyl); alkenyl (preferably (C_2-C_7)alkenyl or heteroalkenyl); alkynyl (preferably (C_2-C_7)alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl); alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);
- R_3 is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl (preferably (C_1-C_{30})alkyl, (C_1-C_{20})alkyl, (C_1-C_{15})alkyl, (C_1-C_{10})alkyl, (C_1-C_7)alkyl) or heteroalkyl) or alkenyl (preferably (C_1-C_{30})alkenyl, (C_1-C_{20})alkenyl, (C_1-C_{15})alkenyl, (C_1-C_{10})alkenyl, (C_1-C_7)alkenyl) or heteroalkyl);

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Preferred derivatives of adenine include those compounds of the aforementioned structure (II) wherein:

- R_1 and R_2 are the same or different and are hydrogen or alkenyl (preferably (C_2-C_{10})alkenyl or (C_2-C_7)alkenyl or heteralkenyl), either unsubstituted or substituted with one or more of hydroxy; halogen (preferably chloro, fluoro and/or bromo); alkyl (preferably (C_1-C_7)alkyl or heteroalkyl); alkenyl (preferably (C_2-C_7)alkenyl or heteroalkenyl); alkynyl (preferably (C_2-C_7)alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl); alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);
- R_3 is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl (preferably (C_1-C_{30})alkyl, (C_1-C_{20})alkyl, (C_1-C_{15})alkyl, (C_1-C_{10})alkyl, (C_1-C_7)alkyl) or heteroalkyl) or alkenyl (preferably (C_1-C_{30})alkenyl, (C_1-C_{20})alkenyl, (C_1-C_{15})alkenyl, (C_1-C_{10})alkenyl, (C_1-C_7)alkenyl) or heteroalkyl);

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Particularly preferred derivatives of adenine include those compounds of the aforementioned structure (II) wherein:

- R_1 and R_2 are the same or different and are hydrogen or acyl;
- R_3 is hydrogen or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl or alkenyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

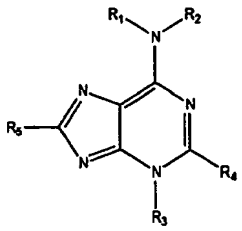
wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

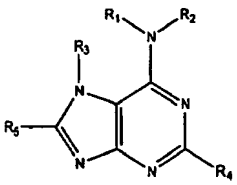
Particularly preferred embodiments of the aforementioned structure (II) include those derivatives of adenine having R_1, R_2, R_3, R_4 and R_5 as defined in Table 2:

2 **Table 2 – Preferred Adenine Derivatives**

Structure	R_1	R_2	R_3	R_4	R_5
(II-a)	Acyl	H	H	H	H
(II-b)	Acyl	H	Saccharide	H	H
(II-c)	Acyl	Alkyl	H	H	H
(II-d)	Acyl	Alkyl	Saccharide	H	H
(II-e)	Acyl	H	H	Alkyl	H
(II-f)	Acyl	H	H	Alkyl	Alkyl
(II-g)	Heteroacyl	H	Saccharide	H	H
(II-h)	Aryl	H	H	H	H
(II-i)	Aryl	H	Saccharide	H	H
(II-j)	Aryl	Alkyl	H	H	H
(II-k)	Aryl	Alkyl	Saccharide	H	H
(II-l)	Aryl	H	H	Alkyl	H
(II-m)	Alkyl	H	H	H	H
(II-n)	Alkyl	H	Saccharide	H	H
(II-o)	Alkyl	Alkyl	H	H	H
(II-p)	Alkyl	Alkyl	Saccharide	H	H
(II-q)	Alkyl	H	H	Alkyl	H

Particularly prefered tautomers of structure (II) are those adenine derivatives having the following structures:





and/or a racemate, enantiomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein R_1, R_2, R_3, R_4 and R_5 are as defined in any above embodiment of an adenine derivatives having aforementioned structure (II) and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

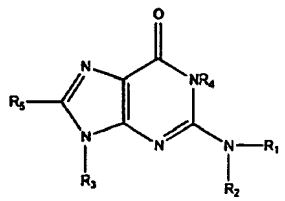
Preferred embodiments of contemplated adenine derivatives include acyl-adenosines and acyl-adenines. Particularly preferred embodiments of contemplated adenine derivatives are mono-acyl-adenosines and mono-acyl-adenines. Preferred embodiments of contemplated adenine derivatives include heteroacyl-adenosines and heteroacyl-adenines. Preferred embodiments of contemplated adenine derivatives include mono-heteroacyl-adenosines and mono-heteroacyl-adenines. Particularly preferred embodiments of contemplated adenine derivatives further include N6-acyl-adenine and N6-acyl-adenosine. Particularly preferred embodiments of contemplated adenine derivatives further include N6-heteroacyl-adenine and N6-heteroacyl-adenosine. Especially preferred embodiments of

contemplated adenine derivatives further include N6-acetyl-adenine and N6-acetyl-adenosine.

Additional preferred embodiments contemplated by the instant invention include racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs, salts (including alternative salts, as well as pharmaceutically acceptable salts, including alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of any of the aforementioned contemplated derivatives of adenine described in this subsection ("Adenine Derivatives").

Guanine Derivatives

Contemplated compounds of the invention additionally include derivatives of guanine defined by the following structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;

- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Preferred derivatives of guanine include those compounds of the aforementioned structure (III) wherein:

- R_1 and R_2 are the same or different and are hydrogen or alkyl (preferably (C_1-C_{10})alkyl or (C_1-C_7)alkyl or heteroalkyl), either unsubstituted or substituted with one or more hydroxy; halogen (preferably chloro, fluoro and/or bromo); alkyl (preferably (C_1-C_7)alkyl or heteroalkyl); alkenyl (preferably (C_2-C_7)alkenyl or heteroalkenyl); alkynyl (preferably (C_2-C_7)alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl); alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);
- R_3 is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and

- R_4 and R_5 are the same or different and are individually hydrogen, alkyl (preferably $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{20})$alkyl, $(C_1\text{-}C_{15})$alkyl, $(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_7)$alkyl) or heteroalkyl) or alkenyl (preferably $(C_1\text{-}C_{30})$alkenyl, $(C_1\text{-}C_{20})$alkenyl, $(C_1\text{-}C_{15})$alkenyl, $(C_1\text{-}C_{10})$alkenyl, $(C_1\text{-}C_7)$alkenyl) or heteroalkyl);

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Preferred derivatives of guanine include those compounds of the aforementioned structure (III) wherein:

- R_1 and R_2 are the same or different and are hydrogen or alkenyl (preferably $(C_2\text{-}C_{10})$alkenyl or $(C_2\text{-}C_7)$alkenyl or heteralkenyl), either unsubstituted or substituted with one or more of hydroxy; halogen (preferably chloro, fluoro and/or bromo); alkyl (preferably $(C_1\text{-}C_7)$alkyl or heteroalkyl); alkenyl (preferably $(C_2\text{-}C_7)$alkenyl or heteroalkenyl); alkynyl (preferably $(C_2\text{-}C_7)$alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl); alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);

- R_3 is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl (preferably $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{20})$alkyl, $(C_1\text{-}C_{15})$alkyl, $(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_7)$alkyl) or heteroalkyl) or alkenyl (preferably $(C_1\text{-}C_{30})$alkenyl, $(C_1\text{-}C_{20})$alkenyl, $(C_1\text{-}C_{15})$alkenyl, $(C_1\text{-}C_{10})$alkenyl, $(C_1\text{-}C_7)$alkenyl) or heteroalkyl);

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Particularly preferred derivatives of guanine include those compounds of the aforementioned structure (III) wherein:

- R_1 and R_2 are the same or different and are hydrogen or acyl;
- R_3 is hydrogen or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl or alkenyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Particularly preferred embodiments of the aforementioned structure (III) include those derivatives of guanine having R_1, R_2, R_3, R_4 and R_5 as defined in Table 3:

Table 3 – Preferred Guanine Derivatives

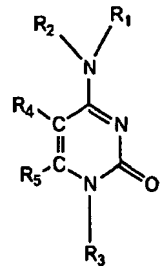
Structure	R_1	R_2	R_3	R_4	R_5
(III-a)	Acyl	H	H	H	H
(III-b)	Acyl	H	Saccharide	H	H
(III-c)	Acyl	Alkyl	H	H	H
(III-d)	Acyl	Alkyl	Saccharide	H	H
(III-e)	Acyl	H	H	H	Alkyl
(III-f)	Acyl	H	H	Alkyl	Alkyl
(III-g)	Heteroacyl	H	Saccharide	H	H
(III-h)	Aryl	H	H	H	H
(III-i)	Aryl	H	Saccharide	H	H
(III-j)	Aryl	Alkyl	H	H	H
(III-k)	Aryl	Alkyl	Saccharide	H	H
(III-l)	Aryl	H	H	H	Alkyl
(III-m)	Alkyl	H	H	H	H
(III-n)	Alkyl	H	Saccharide	H	H
(III-o)	Alkyl	Alkyl	H	H	H
(III-p)	Alkyl	Alkyl	Saccharide	H	H
(III-q)	Alkyl	H	H	H	Alkyl

Preferred embodiments of contemplated guanine derivatives include acyl-guanines and acyl-guanosines. Particularly preferred embodiments of contemplated guanine derivatives mono-acyl-guanines and mono-acyl-guanosines. Preferred embodiments of contemplated guanine derivatives include heteroacyl-guanines and heteroacyl-guanosines. Preferred embodiments of contemplated guanine derivatives include mono-heteroacyl-guanines and mono-heteroacyl-guanosines. Particularly preferred embodiments of contemplated guanine derivatives further include N2-acyl-guanine and N2-acyl-guanosine. Particularly preferred embodiments of contemplated guanine derivatives further include N2-heteroacyl-guanine and N2-heteroacyl-guanosine. Especially preferred embodiments of contemplated guanine derivatives further include N2-acetyl-guanine and N2-acetyl-guanosine.

Additional preferred embodiments contemplated by the instant invention includeracemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs, salts (including alternative salts, as well as pharmaceutically acceptable salts, including alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of any of the aforementioned contemplated derivatives of guanine described in this subsection ("Guanine Derivatives").

Cytosine Derivatives

Contemplated compounds of the invention include derivatives of cytosine defined by the following structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Preferred derivatives of cytosine include those compounds of the aforementioned structure (IV) wherein:

- R_1 and R_2 are the same or different and are hydrogen or alkyl (preferably (C_1-C_{10})alkyl or (C_1-C_7)alkyl or heteroalkyl), either unsubstituted or substituted with one or more hydroxy; halogen (preferably chloro, fluoro and/or bromo); alkyl (preferably (C_1-C_7)alkyl or heteroalkyl); alkenyl (preferably (C_2-C_7)alkenyl or heteroalkenyl); alkynyl (preferably (C_2-C_7)alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl); alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);
- R_3 is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl (preferably (C_1-C_{30})alkyl, (C_1-C_{20})alkyl, (C_1-C_{15})alkyl, (C_1-C_{10})alkyl, (C_1-C_7)alkyl) or heteroalkyl) or alkenyl (preferably (C_1-C_{30})alkenyl, (C_1-C_{20})alkenyl, (C_1-C_{15})alkenyl, (C_1-C_{10})alkenyl, (C_1-C_7)alkenyl) or heteroalkyl);

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Preferred derivatives of cytosine include those compounds of the aforementioned structure (IV) wherein:

- R_1 and R_2 are the same or different and are hydrogen or alkenyl (preferably $(C_2\text{-}C_{10})$alkenyl or $(C_2\text{-}C_7)$alkenyl or heteralkenyl), either unsubstituted or substituted with one or more of hydroxy; halogen (preferably chloro, fluoro and/or bromo); alkyl (preferably $(C_1\text{-}C_7)$alkyl or heteroalkyl); alkenyl (preferably $(C_2\text{-}C_7)$alkenyl or heteroalkenyl); alkynyl (preferably $(C_2\text{-}C_7)$alkynyl or heteroalkynyl); acyl; heteroacyl; aryl (preferably phenyl and/or naphthyl); alkaryl; aralkyl; cycloalkyl (preferably cyclopropyl, cyclopentyl, cyclohexyl and/or cycloheptyl); cycloalkenyl (preferably cyclopropenyl, cyclobutenyl, cyclopentenyl and/or cyclohexenyl); and/or heterocyclic (preferably pyridyl, pyrimidyl, pyranyl, thienyl, furfuryl, pyrrolidyl and/or morpholino);
- R_3 is hydrogen or saccharide (preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl); and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl (preferably $(C_1\text{-}C_{30})$alkyl, $(C_1\text{-}C_{20})$alkyl, $(C_1\text{-}C_{15})$alkyl, $(C_1\text{-}C_{10})$alkyl, $(C_1\text{-}C_7)$alkyl) or heteroalkyl) or alkenyl (preferably $(C_1\text{-}C_{30})$alkenyl, $(C_1\text{-}C_{20})$alkenyl, $(C_1\text{-}C_{15})$alkenyl, $(C_1\text{-}C_{10})$alkenyl, $(C_1\text{-}C_7)$alkenyl) or heteroalkyl);

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Particularly preferred derivatives of cytosine include those compounds of the aforementioned structure (IV) wherein:

- R_1 and R_2 are the same or different and are hydrogen or acyl;
- R_3 is hydrogen or saccharide, preferably ribosyl, deoxyribosyl, 5'phospho-ribosyl, 5'phospho-deoxyribosyl, or glucosyl; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl or alkenyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

Particularly preferred embodiments of the aforementioned structure (IV) include those derivatives of cytosine having R_1, R_2, R_3, R_4 and R_5 as defined in Table 4:

Table 4 – Preferred Cytosine Derivatives

Structure	R_1	R_2	R_3	R_4	R_5
(IV-a)	Acyl	H	H	H	H
(IV-b)	Acyl	H	Saccharide	H	H
(IV-c)	Acyl	Alkyl	H	H	H
(IV-d)	Acyl	Alkyl	Saccharide	H	H
(IV-e)	Acyl	H	H	H	Alkyl
(IV-f)	Acyl	H	H	Alkyl	Alkyl
(IV-g)	Heteroacyl	H	Saccharide	H	H
(IV-h)	Aryl	H	H	H	H
(IV-i)	Aryl	H	Saccharide	H	H
(IV-j)	Aryl	Alkyl	H	H	H
(IV-k)	Aryl	Alkyl	Saccharide	H	H
(IV-l)	Aryl	H	H	H	Alkyl
(IV-m)	Alkyl	H	H	H	H
(IV-n)	Alkyl	H	Saccharide	H	H
(IV-o)	Alkyl	Alkyl	H	H	H
(IV-p)	Alkyl	Alkyl	Saccharide	H	H
(IV-q)	Alkyl	H	H	H	Alkyl

Preferred embodiments of contemplated cytosine derivatives include acyl-cytidines and acyl-cytosines. Particularly preferred embodiments of contemplated cytosine

derivatives are mono-acyl-cytidines and mono-acyl-cytosines. Preferred embodiments of contemplated cytosine derivatives include heteroacyl-cytidines and heteroacyl-cytosines. Preferred embodiments of contemplated cytosine derivatives include mono-heteroacyl-cytidines and mono-heteroacyl-cytosines. Particularly preferred embodiments of contemplated cytosine derivatives further include N4-acyl-cytidine and N4-acyl-cytosine. Particularly preferred embodiments of contemplated cytosine derivatives further include N4-heteroacyl-cytidine and N4-heteroacyl -cytosine. Especially preferred embodiments of contemplated cytosine derivatives further include N4-acetyl-cytidine and N4-acetyl-cytosine.

Additional preferred embodiments contemplated by the instant invention include racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts (including alternative salts, as well as pharmaceutically acceptable salts, including alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of any of the aforementioned contemplated derivatives of cytosine described in this subsection ("Cytosine Derivatives").

Purine and Pyrimidine Derivatives

Contemplated purine derivatives and pyrimidine derivatives include the purine derivatives and pyrimidine derivatives set forth above in the structures (I), (II), (III) and (IV). Additional examples of contemplated purine derivatives and/or pyrimidine derivatives, which may include but are not limited to those compounds encompassed by the structures (I), (II), (III) and (IV), are disclosed in one or more of the following references, the entirety of each of which is herein incorporated by reference:

1) Sheikha et al., Nucleosides Nucleotides Nucleic Acids. 2002 Oct;21(10):619-35;

2) Muller et al., Chem Res Toxicol. 1998 May;11(5):454-63;

3) Dolan et al., Cancer Res. 1994 Oct 1;54(19):5123-30;

4) Hua et al., J Med Chem. 1987 Jan;30(1):198-200;

5) Melanoma Res. 2002 Oct;12(5):417-27;

6) Gu et al., Biochemistry. 2002 Jun 11;41(23):7508-18;

7) Buchdahl et al., Melanoma Res. 1998 Apr;8(2):123-30;

8) Debiton et al., Br J Cancer. 1997;76(9):1157-62;

9) Mounetou et al, J Med Chem. 1997 Aug 29;40(18):2902-9;

10) Cussac et al., J Pharmacol Exp Ther. 1994 Dec;271(3):1353-8;

11) Cussac et al., Drug Metab Dispos. 1994 Jul-Aug;22(4):637-42;

12) Bleasdale et al., Chem Res Toxicol. 1993 Jul-Aug;6(4):407-12;

13) Nukaya et al., Chem Pharm Bull (Tokyo). 1993 Apr;41(4):649-53;

14) Langlois et al., J Biol Stand. 1986 Jul;14(3):201-11;

15) Dutta et al., Biochemistry. 1975 Jul 15;14(14):3144-51;

16) Reese et al., J Chem Soc [Perkin 1]. 1972;23:2937-40;

17) Wang et al., J Org Chem. 2002 Nov 29;67(24):8507-12;

18) Kaiya et al., Nucleosides Nucleotides Nucleic Acids. 2002 Jun-Jul;21(6-7):427-33;

19) Muller et al., Chem Res Toxicol. 1998 May;11(5):454-63;

20) Francom et al., J Org Chem. 2003 Jan 24;68(2):666-9;

21) Garcia-Sastre et al., Biochem J. 1991 Jan 15;273(Pt 2):435-41;

22) Vaghefi et al., J Med Chem. 1987 Aug;30(8):1391-9;

23) Thomassen et al., Biochim Biophys Acta. 1983 Apr 22;723(1):114-22;

24) Watanabe et al., Eur J Biochem. 1981 Jul;117(3):553-8;

25) Watanabe et al., Nucleic Acids Symp Ser. 1979;(6):s79-82;

26) Dutta et al., Biochemistry. 1975 Jul 15;14(14):3144-51;

27) Rajabalee et al., Angew Chem Int Ed Engl. 1971 Jan;10(1):74;

28) Rao et al., J Am Chem Soc. 1970 Aug 12;92(16):4963-70;

29) Hall et al., Biochem Biophys Res Commun. 1970 Feb 6;38(3):496-9; and

30) Ingall et al., J. Med Chem., 1999, 42, 213-220.

Preferred embodiments of contemplated purine derivatives and pyrimidine derivatives include acyl-cytidines, acyl-cytosines, acyl-adenosines, acyl-adenines, acyl-guanosines, and acyl-guanines. Preferred embodiments of contemplated purine derivatives and pyrimidine derivatives include heteroacyl-cytidines, heteroacyl-cytosines, heteroacyl-adenosines, heteroacyl-adenines, heteroacyl-guanosines, and heteroacyl-guanines. Particularly preferred embodiments of contemplated purine derivatives and pyrimidine derivatives are mono-acyl-cytidines, mono-acyl-cytosines, mono-acyl-adenosines, mono-acyl-adenines, mono-acyl-guanosines, and mono-acyl-guanines. Particularly preferred embodiments of contemplated purine derivatives and pyrimidine derivatives are a mono-heteroacyl-cytidine, a mono-heteroacyl-cytosine, a mono-heteroacyl-adenosine, a mono-heteroacyl-adenine, a mono-heteroacyl-guanine, and a mono-heteroacyl-guanosine.

Particularly preferred embodiments of contemplated purine derivatives and pyrimidine derivatives further include N6-gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N4-acetyl-cytidine, N4-acetyl-cytosine, N6-benzyl-adenine, N6-benzyl-adenosine, N6-

acetyl-adenine, N6-acetyl-adenosine, kinetin (6-furfurylaminpurine), kinetin riboside, N2-acetyl-guanosine and N2-acetyl-guanine. N2-acyl-guanosine and N2-acyl-guanine derivatives are especially preferred.

Additional non-limiting examples of contemplated purine derivatives and pyrimidine derivatives, which may include but are not limited to those compounds encompassed by the structures (I), (II), (III) and (IV), include one or more of the following purine derivatives and pyrimidine derivatives: 1-methyladenosine; 2-methyladenosine; N6-methyladenosine; 2'-O-methyladenosine; 2-methylthio-N6-methyladenosine; N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenosine; N6-(cis-hydroxyisopentenyl)adenosine; 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine; N6-glycinylcarbamoyladenosine; N6-threonylcarbamoyladenosine; 2-methylthio-N6-threonyl carbamoyladenosine; N6-methyl-N6-threonylcarbamoyladenosine; N6-hydroxynorvalylcarbamoyladenosine; 2-methylthio-N6-hydroxynorvalyl carbamoyladenosine, 2'-O-ribosyladenosine; 3-methylcytidine; 5-methylcytidine; 2'-O-methylcytidine; 2-thiocytidine, N4-acetylcytidine; 5-formylcytidine; 5,2'-O-dimethylcytidine; N4-acetyl-2'-O-methylcytidine; 1-methylguanosine; N2-methylguanosine; 7-methylguanosine; 2'-O-methylguanosine; N2,N2 dimethylguanosine; N2,2'-O-dimethylguanosine; N2,N2,2'-O-trimethylguanosine; 2'-O-ribosylguanosine; 7-cyano-7-deazaguanosine; 7-aminomethyl-7-deazaguanosine; N6,N6-dimethyladenosine; 2'-O-methylinosine; N4-methylcytidine; N4,2'-O-dimethylcytidine ; N6,2'-O-dimethyladenosine; N6,N6,O-2'-trimethyladenosine; N2 ,7-dimethylguanosine; N2 ,N2 ,7-trimethylguanosine; and 5-formyl-2'-O-methylcytidine.

Additional non-limiting examples of contemplated compounds, which may include but are not limited to those compounds encompassed by the structures (I), (II), (III) and

(IV), include the purine derivatives and pyrimidine derivatives disclosed in the following patents and published patent applications, each of which is herein incorporated by reference: US Patent 3,988,338; US Patent 4,581,056; US Patent 5,075,445; US Patent 5,412,088; US Patent 4,199,574; US Patent 4,748,177; EP 0 224 722 A1; US Patent 5,057,517; EP 1 258 247 A1; WO 02/092093 A1; US Patent 6,294,522; Published US Application 2002/0045595A1; US Patent 6,258,793; Published US Application 2002/0037872A1; EP 1 054 012 A1; EP 1 300 147 A1; US Patent 6,348,451; US Patent 6,525,083; WO 01/40246 A1; US Patent 6,316,426; Published US Application 2002/0035086A1; US Patent 5,066,655; US Patent 5,565,565; US Patent 5,565,566; US Patent 6,429,315; US Patent 6,344,447; WO 00/40584 A1; WO 01/40246 A1; and WO 91/13082 A1.

Additional contemplated compounds of the instant invention include racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts (including alternative salts, as well as pharmaceutically acceptable salts, including alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of any one or more the compounds described in this section (Section B: "Compounds of the Invention") of the instant application. Among the contemplated compounds are activators of AMPK and/or Akt.

Preferred acyl substituent groups on a hydroxyl group, including one or more hydroxyl groups of a saccharide moiety when present, are fatty acids with 6 to 16 carbon atoms, or dicarboxylic acids with 4 to 6 carbon atoms, e.g., succinic, glutaric, or adipic acids. Preferred substituents on an amine group, especially an exocyclic amine group, include amino acids with basic side chains, e.g., lysine or arginine. Other preferred substituents on an amine include acetic acid, nicotinic acid and para-aminobenzoic acid.

Contemplated derivatives of purines and pyrimidines may be synthesized by methods well known in the art. Non-limiting examples of such known methods are disclosed in the following patents and published patent applications, each of which is herein incorporated by reference: US Patent 5,075,445; US Patent 5,412,088; US Patent 4,199,574; US Patent 4,748,177; EP 0 224 722 A1; US Patent 5,057,517; EP 1 258 247 A1; WO 02/092093 A1; US Patent 6,294,522; Published US Application 2002/0045595A1; US Patent 6,258,793; Published US Application 2002/0037872A1; EP 1 054 012 A1; EP 1 300 147 A1; US Patent 6,348,451; US Patent 6,525,083; WO 01/40246 A1; US Patent 6,316,426; Published US Application 2002/0035086A1; US Patent 5,066,655; US Patent 5,565,565; US Patent 5,565,566; US Patent 6,429,315; US Patent 6,344,447; WO 00/40584 A1; WO 01/40246 A1; WO 91/13082 A1. Additionally, the synthesis of N-Acetyl-3',5'-di-O-acetyl-2'-deoxyadenosine has been described by M.J. Robins and R.K. Robins in Interscience Publishers, 1968, pp 519-520 (edited by W.W. Zorbach and R.S. Tipson), the entirety of which is herein incorporated by reference; the synthesis of acyl-cytosines has been described by D. M. Brown, A. Todd and S. Varadarajan in J. Chem. Sc., pp 2384-2387, 1956, the entirety of which is herein incorporated by reference; the synthesis of N-acetyl-2'deoxycytidine has been described in Synthetic Procedures in Nucleic Acid Chemistry, edited by W.W. Zorbach and R.S. Tipson, Interscience Publishers, 1968, p.285-287, the entirety of which is herein incorporated by reference; the synthesis of N-4-Acetyl cytosine nucleosides has been described by M. Ariatti and P.A. Jones, Biochemistry International, 15(6), pp.1097-1103 (1987), the entirety of which is herein incorporated by reference; and the synthesis of N-4-acetyl-cytidine has been described by K.A. Watanabe and J.J. Fox in

Angew. Chem. Internat.Edit. 5(6), pp 579-580 (1966), the entirety of which is herein incorporated by reference.

Well-known methods for synthesizing acylated derivatives of purines and pyrimidines include reacting a purine or a pyrimidine, or a congener of either, with an activated carboxylic acid, such as a carboxylic acid that has been treated with appropriate reagents to render its carboxylate carbon more susceptible to nucleophilic attack than is the case in the original carboxylic acid. Well known examples of useful activated carboxylic acids for synthesis of the compounds of the invention are acid chlorides, acid anhydrides, n-hydroxysuccinimide esters, or carboxylic acids activated with BOP-DC. Carboxylic acids may also be linked to a purine or a pyrimidine, or a congener of either, with coupling reagents like dicyclohexylcarbodiimide (DCC).

During preparation of the acyl compounds contemplated by the invention, when the acid source of the desired acyl derivative has groups which interfere with the acylation reactions, e.g., hydroxyl or amino groups, these groups may be blocked with protecting groups, e.g., t-butyldimethylsilyl ethers or t-BOC groups, respectively, before preparation of the anhydride. For example, lactic acid may be converted to 2-t-butyldimethylsiloxypropionic acid with t-butyldimethylchlorosilane, followed by hydrolysis of the resulting silyl ester with aqueous base. The anhydride may be formed by reacting the protected acid with DCC. With amino acids, the N-t-BOC derivative may be prepared using standard techniques, which derivative may then converted to the anhydride with DCC. With acids containing more than one carboxylate group (e.g., succinic, fumaric, or adipic acid) the acid anhydride of the desired dicarboxylic acid may be, for example, reacted with a purine or pyrimidine in pyridine or pyridine plus dimethylformamide or dimethylacetamide.

Amino acids may be coupled to the exocyclic amino groups, such as those of cytidine, and to hydroxyl groups, such as those on the aldose moiety of nucleosides or their congeners, using DCC in a suitable solvent, particularly a mixture of (i) methylene chloride and (ii) dimethylacetamide or dimethylformamide, for example.

Carbyloxycarbonyl derivatives of a purine or pyrimidine, or a congener of either, may be prepared by reacting with the appropriate carbylchloroformate in a solvent such as pyridine or pyridine plus dimethylformamide under anhydrous conditions, for example. The solvent may be removed under vacuum, and the residue purified by column chromatography.

In still further alternative aspects, it should be appreciated that certain of the contemplated compounds, in addition to being synthesized in vitro, may also be isolated from natural sources. Preferred natural sources include *Hordeum vulgare* or malted seed therefrom. Other preferred natural sources include *Hordeum sativum, Hordeum jubatum, Hordeum murinum,* or malted seed therefrom. Contemplated compounds also include purine derivatives and pyrimidine derivatives, in substantially pure form, obtainable through purification from natural sources. Particularly preferred natural sources include malted barley seed extracts and brewer's yeast extracts.

Among preferred naturally occurring derivatives contemplated by the invention are the cytokinins. Plants are particularly rich sources of various cytokinins, with *Hordeum vulgare,* or malted seed therefrom, being a particularly preferred source for obtaining various cytokinins. Other preferred natural sources include *Hordeum sativum, Hordeum jubatum, Hordeum murinum,* or malted seed therefrom. Especially preferred sources from which such substantially pure compounds may be purified include the malted barley seed

extracts disclosed in WO 01/66146 A1, WO 02/072148 A1, and U.S. Provisional Patent Application 60/408,887, the entireties of which are herein incorporated by reference. Consequently, it should be appreciated that contemplated compounds may be entirely or partially synthesized/modified. For example, where contemplated compounds are partially synthesized, a precursor of contemplated compounds may be isolated from a plant or microorganism, and then subjected to one or more steps to arrive at a contemplated compound. Contemplated compounds may be modified in one or more synthetic steps to impart a particularly desirable physico-chemical property. For example, contemplated compounds may be esterified with a polar compound (*e.g.*, polyethylene glycol) to increase water solubility. In another example, contemplated compounds may be coupled to a resin or other material to control the rate of release to the organism.

The forgoing are illustrative, and not limiting, examples of methods and sources that can be used to prepare and/or obtain the contemplated compounds and compositions of the present invention. Thus, it will be understood to the person skilled in the art that other methods and sources can be used to prepare and/or obtain the contemplated compounds and compositions of the invention.

C. Assay and Screening Methods of the Invention

Among the embodiments of the instant invention are methods for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), such methods comprising: 1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and 2) measuring an indicator of AMPK activity to determine the degree to

which the candidate compound activates AMPK; wherein the candidate compound is a cytokinin of structure (I), an adenine derivative of structure (II), a guanine derivative of structure (III), and/or a cytosine derivative of structure (IV). In a preferred embodiment of such a method, the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins of structure (I), two or more different adenine derivatives of structure (II), two or more different guanine derivatives of structure (III) or two or more different cytosine derivatives of structure (IV). In a preferred embodiment, measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK results in a test value being determined, where the test value is compared with a corresponding control value, which as would be readily apparent to one of skill in the art, is a value determined under the same or similar conditions as the test value, but in the absence of, or in the presence of a reduced concentration of, the candidate compound.

As would be apparent to one of skill in the art, such methods for determining the degree to which a candidate compound activates AMPK in certain cell types and/or tissue types find utility in assessing the potential of certain compounds of the invention as drugs useful in treating a variety of disorders that are ameliorated through activation of AMPK in certain cell types and/or tissue types, such as those disorders well known in the art and/or exemplified in the instant application. The contemplated methods are also suitable for use in screening methods for identifying drugs useful in treating a variety of disorders that are ameliorated through activation of AMPK in certain cell types and/or tissue types, such as those disorders well known in the art and/or exemplified in the instant application.

Various methods are well within the skill of the art for measuring an indicator of AMPK activity to determine the degree to which AMPK is activated under test conditions, and many such methods are well-known. For example, see WO 00/28076 A1, WO 02/09726 A1 and WO 03/037371 A2, the entireties of which are herein incorporated by reference. Such methods include:

1. AMPK has been found to be a heterotrimeric complex composed of a catalytic subunit (alpha) and two regulatory subunits (beta and gamma). Activation of AMPK leads to phosphorylation of the catalytic unit (the alpha unit) on a given residue (Thr 172) that can be identified using specific antibodies reacting with the phosphorylated form of the AMPK alpha unit. Briefly, the ability of a given compound or procedure to activate the AMPK can be evaluated by its ability to induce phosphorylation of the Thr 172 residues on the AMPK catalytic subunit. (For a recent example, see Fryer LG, Parbu-Patel and Carling, J. Biol. Chem 2002 277:25226 the entirety of which are herein incorporated by reference.)

2. Further, activation of AMPK is well-known to increase glucose uptake in several cell lines and tissues. Upon activation, AMPK induces glucose uptake that can be monitored using a radioactive ligand (glucose or glucose mimetic). Briefly, the ability of a given compound or procedure to activate the AMPK can be evaluated by its ability to increase glucose uptake in a given cell line or tissue. (See Abbud W, Habinowski S, Zhang JZ, Kendrew J, Elkairi FS, Kemp BE, Witters LA, Ismail-Beigi F, Arch Biochem Biophys 2000 380:347, the entirety of which are herein incorporated by reference.)

3. Evaluation of the ability of AMPK, a serine/threonine protein kinase, to phosphorylate *in vivo* or *in vitro* a given substrate. Typically, in these experiments the substrate is a protein or a peptide containing a sequence similar to the sequence surrounding

the site phosphorylated by AMPK on its natural substrates. The AMARA peptide (AMARAASAAALARRR) and the SAMS peptide (HMRSAMSGLHLVKRR) are typically used as substrates in these studies. Briefly, AMPK-containing cell extracts or purified forms of the AMPK are incubated in the presence of a substrate, an adequate reaction mix and a tracer, usually a phosphorylated form of ATP. (For an example, see Davies et al., S. P., Carling, D. and Hardie, D. G. (1989) Eur. J. Biochem. 186. 123-128, the entirety of which are herein incorporated by reference.) More recently, eNOS, nNOS and nNOSμ have been proposed as substrates for assessing AMPK activity the presence of putative AMPK activators. (For example, see WO 00/28076 A1) In the case of eNOS, phosphorylation of threonine 495 in the presence of limiting calcium has been suggested as a measure to be assessed, and in the case of nNOS and nNOSμ, phosphorylation of Serine-1417 is suggested as a measure to be assessed.

As one of skill in the art would recognize, a wide a variety of cell types and/or tissue types that express AMPK, or that are capable of expressing AMPK, may be employed in the methods of the invention. Preferred cell types and/or tissue types include one or more of myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue. Other preferred cell types include one or more of 3T3-LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells. Especially preferred cell lines for Western immunoblotting include the C2C12 mouse muscle cells (from ATTC) as well as in primary culture of human skeletal muscle cells (from Clonetics, Inc.)

Among the embodiments of the instant invention are methods for determining the degree to which a candidate compound activates Akt, where such methods comprise: 1)

contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and 2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt; wherein the candidate compound is a cytokinin of structure (I), an adenine derivative of structure (II), a guanine derivative of structure (III), and/or a cytosine derivative of structure (IV). In a preferred embodiment of such a method, the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins of structure (I), two or more different adenine derivatives of structure (II), two or more different guanine derivatives of structure (III) or two or more different cytosine derivatives of structure (IV). In a preferred embodiment, measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt results in a test value being determined, where the test value is compared with a corresponding control value, which as would be readily apparent to one of skill in the art, is a value determined under the same or similar conditions as the test value, but in the absence of, or in the presence of a reduced concentration of, the candidate compound.

As would be apparent to one of skill in the art, such methods for determining the degree to which a candidate compound activates Akt in certain cell types and/or tissue types find utility in assessing the potential of certain compounds of the invention as drugs useful in treating a variety of disorders that are ameliorated through activation of Akt in certain cell types and/or tissue types, such as those disorders well known in the art and/or exemplified in the instant application. The contemplated methods are also suitable for use in screening methods for identifying drugs useful in treating a variety of disorders that are ameliorated

through activation of Akt in certain cell types and/or tissue types, such as those disorders well known in the art and/or exemplified in the instant application.

Various methods are well within the skill of the art for measuring an indicator of Akt activity to determine the degree to which Akt is activated under test conditions, and many such methods are well-known. In general, such methods are analogous to the above described methods that rely on measuring an indicator of AMPK activity for determining the degree to which the candidate compound activates AMPK. For example, measuring the phosphorylation of the serine 473 residue of Akt is a method that is well within the skill of the art, and well-known, for measuring an indicator of Akt activity for determining the degree to which Akt is activated under test conditions. As one of skill in the art would recognize, a wide variety of cell types and/or tissue types that express Akt, or that are capable of expressing Akt, may be employed in the methods of the invention. Preferred cell types and/or tissue types include one or more of myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue. Other preferred cell types include one or more of 3T3-LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells. Especially preferred cell lines for Western immunoblotting include the C2C12 mouse muscle cells (from ATTC) as well as in primary culture of human skeletal muscle cells (from Clonetics, Inc.)

Among the embodiments of the instant invention are methods for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising: 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and 2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound

increases Glut-4 content; wherein the candidate compound is a cytokinin of structure (I), an adenine derivative of structure (II), a guanine derivative of structure (III), and/or a cytosine derivative of structure (IV). In a preferred embodiment of such a method, the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins of structure (I), two or more different adenine derivatives of structure (II), two or more different guanine derivatives of structure (III) or two or more different cytosine derivatives of structure (IV). In a preferred embodiment, measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content results in a test value being determined, where the test value is compared with a corresponding control value, which as would be readily apparent to one of skill in the art, is a value determined under the same or similar conditions as the test value, but in the absence of, or in the presence of a reduced concentration of, the candidate compound.

As would be apparent to one of skill in the art, such methods for determining the degree to which a candidate compound increases Glut-4 content in certain cell types and/or tissue types find utility in assessing the potential of certain compounds of the invention as drugs useful in treating a variety of disorders that are ameliorated through increasing Glut-4 content in certain cell types and/or tissue types, such as those disorders well known in the art and/or exemplified in the instant application. The contemplated methods are also suitable for use in screening methods for identifying drugs useful in treating a variety of disorders that are ameliorated through increasing Glut-4 content in certain cell types and/or tissue types, such as those disorders well known in the art and/or exemplified in the instant application.

Various methods are well within the skill of the art for measuring an indicator of Glut-4 content to determine the degree to which Glut-4 is activated under test conditions, and many such methods are well-known. For example, antibodies raised against Glut-4 are readily available for measuring Glut-4 content by Western immunoblotting. The use of such antibodies in Western immunoblotting assays is well within the skill of the art, and well-known, for measuring an indicator of Glut-4 content for determining the degree to which the candidate compound increases Glut-4 content under test conditions. As one of skill in the art would recognize, a wide variety of cell types and/or tissue types that express Glut-4, or that are capable of expressing Glut-4, may be employed in the methods of the invention. Preferred cell types and/or tissue types include one or more of myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue. Other preferred cell types include one or more of 3T3-LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells. Especially preferred cell lines for Western immunoblotting include the C2C12 mouse muscle cells (from ATTC) as well as in primary culture of human skeletal muscle cells (from Clonetics, Inc.)

Among the embodiments of the instant invention are methods for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising: 1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and 2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell; wherein the candidate compound is a cytokinin of structure (I), an adenine derivative of

structure (II), a guanine derivative of structure (III), and/or a cytosine derivative of structure (IV). In a preferred embodiment of such a method, the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins of structure (I), two or more different adenine derivatives of structure (II), two or more different guanine derivatives of structure (III) or two or more different cytosine derivatives of structure (IV). In a preferred embodiment, measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell results in a test value being determined, where the test value is compared with a corresponding control value, which as would be readily apparent to one of skill in the art, is a value determined under the same or similar conditions as the test value, but in the absence of, or in the presence of a reduced concentration of, the candidate compound.

As would be apparent to one of skill in the art, such methods for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell in certain cell types and/or tissue types find utility in assessing the potential of certain compounds of the invention as drugs useful in treating a variety of disorders that are ameliorated through enhancing translocation of Glut-4 from an intracellular location to the plasma membrane of a cell in certain cell types and/or tissue types, such as those disorders well known in the art and/or exemplified in the instant application. The contemplated methods are also suitable for use in screening methods for identifying drugs useful in treating a variety of such disorders that are ameliorated through enhancing translocation of Glut-4 from an intracellular location to the

plasma membrane of a cell in certain cell types and/or tissue types, such as those disorders well known in the art and/or exemplified in the instant application.

Various methods are well within the skill of the art for measuring an indicator of Glut-4 translocation to determine the degree to which translocation of Glut-4 from an intracellular location to the plasma membrane of a cell is enhanced under test conditions, and many of such methods are well-known. For example, see US 6,303,373, the entirety of which is herein incorporated by reference, for a representative disclosure of a method for measuring an indicator of Glut-4 translocation to determine the degree to which translocation of Glut-4 from an intracellular location to the plasma membrane of a cell is enhanced under test conditions. As one of skill in the art would recognize, a wide variety of cell types and/or tissue types that express Glut-4, or that are capable of expressing Glut-4, may be employed in the methods of the invention. Preferred cell types and/or tissue types include one or more of myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue. Other preferred cell types include one or more of 3T3-LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells. Especially preferred cell lines for include the C2C12 mouse muscle cells (from ATTC) as well as in primary culture of human skeletal muscle cells (from Clonetics, Inc.)

D. Pharmaceutical Compositions and Dietary Supplements of the Invention

In another aspect, a preferred embodiment of the present invention provides a pharmaceutical and/or nutraceutical that comprises a therapeutically effective amount of one or more of the contemplated compounds of Section B ("Compounds of the Invention") formulated together with one or more pharmaceutically acceptable carriers, including additives and/or excipients and/or diluents.

As described in detail herein, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including preferred embodiments adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; or (3) topical application, for example, as a cream, ointment or spray applied to the skin.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual) and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent of the weight of a single dosage form, active ingredient will range from about 0.01

per cent to about ninety-nine percent of the total weight, more preferably from about 0.05 per cent to about 90 per cent, more preferably from about 0.1 per cent to about 90 per cent, more preferably from about 0.5 per cent to about 85 per cent, more preferably from about 1 per cent to about 80 per cent, more preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent. In preferred embodiments, the weight of active ingredient will constitute at least a certain percentage of the total weight of the single dosage form, the certain percentage being selected from one or more or the following: about 0.01%, about 0.05%, about 0.1%, about 0.5%, about 1%, about 2%, about 3%, about 4%, about 5%, about 7.5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95% or about 99%. In certain preferred embodiments, the weight of active ingredient will constitute no more than a certain percentage of the total weight of the single dosage form, the certain percentage being selected from one or more or the following: about 0.01%, about 0.05%, about 0.1%, about 0.5%, about 1%, about 2%, about 3%, about 4%, about 5%, about 7.5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95% or about 99%.

Methods of preparing these formulations or compositions include the step of bringing into association a contemplated compound (or compounds) of the present invention with the carrier and/or one or more accessory ingredients. In preferred embodiments, the contemplated compound is substantially pure prior to being brought into association with the carrier and/or one or more accessory ingredients.

In general, the formulations are prepared by uniformly and intimately bringing into association a contemplated compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

An oral route of administration is preferred for the pharmaceuticals, including nutraceuticals, of the invention. Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as bronchoaveolar lavages for intended delivery systems to the lung and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In a preferred embodiments to prepare an orally administerable solid dosage form (e.g. capsules, tablets, pills, dragees, powders, granules and the like), an active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any other pharmaceutically acceptable carriers such as: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such

as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) coloring agents: (11) phosphate-buffered saline solution (12) emulsions, such as an oil/water or water/oil emulsion; (12) adjuvants; and (13) sterile aqueous solutions, for example. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile

solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar--agar and tragacanth, and mixtures thereof.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the

compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

When the compounds of the present invention are administered to humans or other animals, they can be given *per se* or as a pharmaceutical composition comprising the active ingredient(s) and a pharmaceutically acceptable carrier. In preferred embodiments, the active ingredient or ingredients represent, in total, about 0.01 to about 99.5% by weight (more preferably, about 0.5 to about 90% by weight) of the total formulation, for example. In particularly preferred embodiments, the active ingredient represents at least about 0.01%, about 0.05%, about 0.1%, about 0.5%, about 1%, about 2%, about 3%, about 4%, about 5%,

about 7.5%, about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95% or about 99% by weight of the pharmaceutical composition.

The preparations of the present invention may be given by routes including oral, parenteral, and topical routes. They are of course given by forms suitable for each administration route. Oral administration is preferred. And the preferred form for oral administration is tablet or capsule.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, doses of the compounds of this invention for a patient, when used for the indicated effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably from about 0.1 to about 40 mg per kg per day.

In preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will range from about 0.001 mg to about 1000 mg, more preferably from about 0.01 mg to about 500 mg, still more preferably from about 0.01 mg to about 100 mg, still more preferably from about 0.01 mg to about 10 mg, still more preferably from about 0.01 mg to about 1 mg. In preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will range from about from about 0.1 mg to about 10 mg. In preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will range from about from about 0.1 mg to about 1 mg. In preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will

range from about from about 1 mg to about 10 mg. In preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will range from about from about 10 mg to about 25 mg. In preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will range from about from about 25 mg to about 50 mg. In preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will range from about from about 50 mg to about 100 mg. In preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will be selected from one or more of about 0.001 mg, about 0.01 mg, about 0.1 mg, about 0.25 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 2 mg, about 2.5 mg, about 5 mg, about 7.5 mg, about 10 mg, about 15 mg, about 20 mg, about 50 mg, about 100 mg, about 200 mg, about 500 mg and about 1,000 mg.

In preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will be selected from amount sufficient to increase, following oral or parenteral administration of said unit dosage to a patient in need thereof, an intracellular level of activated AMPK and/or an intracellular level of activated Akt in one or more cell types and/or tissue types of said patient. In especially preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will be selected from an amount sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least about 20% over pre-administration levels. In other preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will be selected from an amount sufficient to increase,

over pre-administration levels, the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least about 30%, at least about 50%, at least about 75%, at least about two-fold, at least about four-fold, or at least about ten-fold. In other preferred embodiments, a unit dose of the compound of this invention for a patient, when used for the indicated effects, will be selected from an amount sufficient to increase, over pre-administration levels, the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by up to about 30%, up to about 50%, up to about 75%, up to about two-fold, up to about four-fold, up to about ten-fold or up to about fifteen-fold.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical composition, where the pharmaceutical composition comprises, or preferably consists essentially of, one or contemplated compounds, a pharmaceutically acceptable carrier, and optionally, one or more additional therapeutic ingredients. It is especially preferred that a compound of the invention be administered in the form of a substantially pure pharmaceutical composition.

The pharmaceutical compositions of the instant invention comprise one or more of the contemplated purine derivatives, including cytokinins, adenine derivatives, and guanine derivatives, and/or one or more pyrimidine derivatives, including cytosine derivatives, as disclosed in Section B ("Compounds of the Invention") of the instant application.

Cytokinins, adenine derivatives, guanine derivatives, and cytosine derivatives preferred for use in the pharmaceutical compositions of the instant invention include those set forth in the aforementioned structures (I), (II), (III) and (IV), respectively, as well as racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts (including alternative salts, as well as pharmaceutically acceptable salts, including alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives thereof. Contemplated compounds that are preferred for use in the pharmaceutical compositions of the instant invention include a mono-acyl-cytosine, a mono-acyl-adenine, a mono-acyl-adenosine, a mono-acyl-guanosine, and a mono-acyl-guanine, as well as racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts (including alternative salts, as well as pharmaceutically acceptable salts, including alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives thereof, where the contemplated compound is an activator of AMPK and/or Akt. Particularly preferred purine derivatives and pyrimidine derivatives that are activators of AMPK and/or Akt, and that are preferred for use in the pharmaceutical compositions of the instant invention, further include N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin, cis-zeatin; trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N4-acetyl-cytidine, N4-acetyl-cytosine, N6-benzyl-adenine, N6-benzyl-adenosine, N6-acetyl-adenine, N6-acetyl-adenosine, kinetin riboside, kinetin, N2-acetyl-guanosine and N2-acetyl-guanine. N2-acyl-guanosine and N2-acyl-guanine derivatives are especially preferred; as well as racemates, enantiomers, tautomers, solvates, hydrates, pro-drugs, polymorphs salts (including alternative salts, as well as pharmaceutically acceptable salts, including

alternative pharmaceutically acceptable salts), acyl derivatives and/or heteroacyl derivatives of any one or more the aforementioned compounds.

In further aspects of the inventive subject matter, it should be appreciated that contemplated compositions may further comprise additional active ingredients, including compositions known to decrease a blood lipid concentration, and/or compositions known to decrease blood sugar concentrations. For example, additional active ingredients may include at least one of a vitamin and/or mineral preparation (including, but not limited to, chromium and/or vanadium), metformin, sulfonylurea, thiazolidinediones (TZDs) and the like. Preferred additional active ingredients include one or more of metformin, sulfonylurea, pioglitazone and rosiglitazone.

In still further aspects of the invention, contemplated compositions increase glucose uptake into a cell when present in a medium surrounding the cell, such as in the serum or interstitial fluids. It is contemplated that the cell may be any cell including a myocyte or other muscle cells, or part of a tissue. It is further contemplated that the cell may be insulin dependent or insulin independent. Contemplated tissues are preferred to be *in vivo*, and may include liver tissue, skeletal muscle tissue, pancreatic tissue, and adipose tissue. It is further contemplated that the composition may increase glucose uptake into a cell when the compound is present in a medium surrounding the cell at a concentration of between 0.1 to 100 micrograms per milliliter. In a preferred embodiment, the composition may increase glucose uptake into a cell when the compound is present in a medium surrounding the cell at a concentration of between 0.5 to 50 micrograms per milliliter. In another a preferred embodiment, the composition may increase glucose uptake into a cell when the compound is present in a medium surrounding the cell at a concentration of between 2 to 10 micrograms

per milliliter. In a preferred embodiment, 0.1 to 100 micrograms per milliliter. In a preferred embodiment, the composition may increase glucose uptake into a cell when the compound is present in a medium surrounding the cell at a concentration greater than one or more of 0.1, 0.5, 1, 2, 5, 10, 25, 50 and 100 micrograms per milliliter. In a preferred embodiment, the medium is blood. In a preferred embodiment, the medium is plasma.

E. Treatment Methods of the Invention

An advantageous aspect of the instant invention concerns the discovery that, when administered in a therapeutically effective dose, compounds and compositions of the invention, including pharmaceutical compositions, will reduce blood glucose concentrations in an organism suffering from an elevated glucose concentration. While not wishing to be bound by theory, applicants believe a mechanism involving the activation of AMPK and/or Akt underlies the reduction in blood glucose that follows administration of a contemplated compound, or a composition comprising a contemplated compound, including a pharmaceutical composition, to an organism. As such, the utility of the inventive subject matter additionally extends to methods for treating a variety of disorders that are ameliorated through activation of AMPK and/or Akt, such as those disorders well known in the art and/or exemplified in the instant application.

In a preferred aspect of the inventive subject matter, exposing an organism to a contemplated compound, or a composition comprising a contemplated compound, including a pharmaceutical composition, results in increased intracellular levels of activated AMPK and/or activated Akt. In one embodiment, the organism is a tissue or cell isolated from a whole organism. In another embodiment, the organism is a whole organism. In a preferred

embodiment, the organism is a whole human organism or a tissue or cell isolated therefrom. In other preferred embodiments, the cell may be a myocyte or part of an *in vivo* tissue such as liver tissue, skeletal muscle tissue, pancreatic tissue, or adipose tissue. An oocyte is one example of a preferred organism that may be employed in a preferred process, where oocyte activity increases in response to the increased intracellular levels of activated AMPK that result from exposing the organism to the composition. In another preferred embodiment, the cellular import, export or synthesis of a molecule is modulated in response to the increased intracellular levels of activated AMPK and/or activated Akt that result from exposing the organism to a contemplated compound, or a composition comprising a contemplated compound. In a preferred embodiment, exposing the organism to a contemplated compound, or a composition comprising a contemplated compound, increases cellular glucose uptake. In a preferred embodiment, the compound increases glucose uptake in a non-insulin dependent manner. In a further preferred embodiment, the increase in glucose uptake is attenuated by the presence of L-N-mono-methyl-L-arginine at a concentration of 300 micromoles per liter.

In a preferred aspect of the inventive subject matter, a therapeutically effective dose of a pharmaceutical composition, including a pharmaceutical and/or nutraceutical, comprising a contemplated compound is orally administered to a human patient diagnosed with non-insulin dependent diabetes mellitus (NIDDM) and having an elevated glucose concentration. Among the beneficial results contemplated for the treatment is a reduction in blood glucose concentrations in the patient. Thus, an exemplary method comprises treating a person (*e.g.*, diagnosed with NIDDM) having an increased blood concentration of glucose, such as of approximately 150 mg/dl, for example. In a preferred embodiment, a

therapeutically effective dose of a pharmaceutical composition, including a pharmaceutical and/or nutraceutical, comprising a contemplated compound is coadministered along with at least one of a vitamin and/or mineral preparation (including, but not limited to, chromium and/or vanadium), metformin, sulfonylurea, thiazolidinediones (TZDs) and the like. In a preferred embodiment, a pharmaceutical composition, including a pharmaceutical and/or nutraceutical, comprising a contemplated compound is coadministered along with at least one of metformin, sulfonylurea, pioglitazone and rosiglitazone, or any other medication useful in the treatment of diabetes.

With respect to the glucose concentration, it is generally contemplated that the glucose concentration is a blood glucose concentration. However, further contemplated glucose concentrations also include concentrations of glucose covalently or non-covalently bound to molecules found within the organism, and especially contemplated alternative glucose concentrations include concentrations of glycosylated proteins (*e.g.*, glycosylated hemoglobin or collagen).

It should be especially appreciated that contemplated pharmaceutical compositions not only reduce elevated blood glucose concentration in a human suffering from NIDDM, but may also reduce blood glucose concentrations in individuals having elevated blood glucose concentrations for reasons other than NIDDM, including obesity, dietary effects, etc.

Since another advantage to the treatment with the contemplated compounds and compositions, including pharmaceutical compositions, relates to blood concentration of total cholesterol, treatment according to the inventive subject matter need not be limited to patients having elevated blood glucose levels, but may also be indicated in many patients

having near normal blood concentrations of glucose. Thus, a exemplary method comprises treating a person having an increased blood concentration of total cholesterol, such as above 280 mg/dl, for example.

It is especially contemplated that treatment according to the inventive subject matter may also result in significant weight loss, particularly in persons with obesity, NIDDM, or other condition associated with increased body weight. It is generally contemplated that the treatment according to the inventive subject matter is not limited to reduction of blood glucose alone, but may concomitantly, or alternatively, include reduction of a particular lipid or lipid group. For example, slightly elevated total cholesterol (*e.g.*, 220 mg/dl) may be an indication for treatment with the contemplated compounds and compositions. Alternatively, it is contemplated that an imbalance between HDL and LDL (*i.e.* LDL>>HDL) may be normalized employing a treatment according to the inventive subject matter. Similarly, while the total cholesterol in the patient need not be elevated, treatment with the contemplated method may still be indicated due to an elevated triglyceride level.

Furthermore, contemplated compounds and compositions may also advantageously reduce elevated blood lipid concentrations, wherein blood lipids such as, for example, triglycerides, fatty acids, HDL-cholesterol, and LDL-cholesterol. Moreover, contemplated compositions and compounds include those that may reduce blood lipids concomitantly with the reduction of blood glucose levels, or independent of the reduction of the blood glucose level.

It should also be appreciated that treatment with contemplated compounds and compositions containing them, including pharmaceutical compositions, is expected to diminish, or reduce the rate of progression of, damage to the endothelium caused by

hyperglycemia and free fatty acids, and for this reason it should be useful in preventing and treating various types of vascular disease associated with metabolic abnormalities, including atherosclerotic vascular disease and, in particular, atherosclerosis associated with diabetes and insulin resistance. (For example, see WO 01/10449 A1, the entirety of which is herein incorporated by reference.) By virtue of its effects on glucose and fatty acid metabolism in pericytes, this treatment should also be useful in treating and preventing the microvascular complications of diabetes (such as chronic wounds, blindness, retinopathy and possibly nephropathy). Furthermore, treatment with contemplated compounds and compositions containing them, including pharmaceutical compositions, should also prove a useful tool as a chronically administered therapeutic agent in a wide array of situations in which endothelial cell integrity is compromised by stress, e.g., hyperglycemia, high plasma free fatty acid levels and to the extent they are caused by alterations in glucose or fatty acid metabolism possibly ischemia and inflammation.

Additional preferred embodiments include methods for activating adenosine 5'-monophosphate-activated protein kinase (AMPK) in a patient in need thereof, the method comprising administering to said patient a composition comprising a therapeutically effective amount of a contemplated compound that activates AMPK, wherein the patient suffers from a condition or disorder selected from the group consisting of: non-insulin dependent (type 2) diabetes mellitus, high blood pressure, elevated levels of triglycerides, hyperinsulinemia, glucose intolerance, low levels of high density lipoprotein (HDL), ischemia, hypoxia and glucocorticoid-induced apoptosis.

Preferred embodiments include methods for activating adenosine 5'-monophosphate-activated protein kinase (AMPK) in a patient in need thereof, the method comprising

administering to said patient a composition comprising a therapeutically effective amount of a contemplated compound that activates AMPK, wherein the method results in one or more of the following: (1) reduces one or more of fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression; (2) ameliorates one or more conditions or disorders that are characterized by elevations in one or more of the pathways or mechanisms involved in fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression; (3) increases fatty acid oxidation and ketogenesis; (4) inhibits lipogenesis and/or isoprenaline-stimulated lipolysis; (5) ameliorates one or more conditions or disorders that are characterized by elevations in one or both of lipogenesis and isoprenaline-stimulated lipolysis pathways, or that are exacerbated by the elevations in one or both of these pathways; (6) decreases insulin secretion; (7) ameliorates one or more a conditions or disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion; (8) enhances glucose uptake in muscle cells; (9) ameliorates one or more conditions or disorders that are characterized by decreased glucose uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle cells; (10) reduces levels of cytoplasmic HuR, which in turn, in reduces concentrations and half-lives of target mRNA transcripts; (11) ameliorates one or more conditions or disorders that are characterized decreased levels of HuR and its target transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target transcripts, which may, for example, play an important role in aging; (12) provides protection against glucocorticoid-induced apoptosis; (13) ameliorates one or more conditions or disorders that are characterized by increased glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced apoptosis; (14) protects against cellular

stresses resulting from ischemia; (15) inhibits adipogenesis; (16) ameliorates one or more conditions or disorders that are characterized by increased adipogenesis, or that are exacerbated by adipogenesis; (17) protects neurons against metabolic and excitotoxic insults associated with the pathogenesis of a neurodegenerative condition; (18) promotes astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism; (19) increases insulin sensitivity of muscle glucose transport; (20) protects against hepatic ischemia-reperfusion (I/R) injury associated with liver transplantation and hepatic resections; (21) lowers blood glucose concentrations by decreasing hepatic glucose production and/or increasing glucose disposal in skeletal muscle; and (22) ameliorates one or more conditions or disorders associated with insulin resistance syndrome through improving glucose tolerance, improving lipid profile or reducing systolic blood pressure.

The duration for contemplated treatments may vary significantly, and suitable durations may be within the range of a single dose, but also for a predetermined period, including one week, several weeks, several months, and even several years. Consequently, it should be appreciated that compositions according to the inventive subject matter may also be prophylactically administered to a human to prevent hyperglycemia, or some form of dyslipidemia.

Of course it should also be recognized that the form of administration may vary considerably. For example, oral administration need not be limited to a tablet, and alternative oral administrations may include powders, gel-caps, syrups, gels, etc. Where oral administration is not desirable, it is further contemplated that alternative routes are also appropriate, including injections, transdermal, pulmonary or intranasal delivery. (Various formulations appropriate for use in the contemplated methods are discussed in detail in

Section D - "Pharmaceutical Compositions and Dietary Supplements of the Invention" of the instant application.)

In further alternative aspects of the inventive subject matter, the composition may also be administered to an organism other than a human, and particularly preferred alternative organisms include livestock (*e.g.*, cattle, pigs, horses, etc.) and pets (*e.g.*, dogs, cats, rodents, birds, etc.). With respect to contemplated compound and compositions, the same considerations as described above apply.

Examples

Examples 1-17 exemplify various procedures, results and embodiments related to the contemplated compounds, compositions and methods of the inventive subject matter.

Example 1

The levels of Glut-4, activated AMPK and activated Akt were measured in mouse muscle cells C2C12 (from ATTC) and in primary culture of human skeletal muscle cells (Clonetics, Inc.) using Western immunoblotting. C2C12 cells were plated at 1.5x1-exp5 cells per mL/well (12-well plate) in standard cell culture medium (DMEM supplemented with 10% fetal bovine serum (FBS), 25mM glucose, 20mM Hepes, 4mM glutamine and 2 mM sodium pyruvate. 48 hrs after the plating, medium was changed to differentiation medium (DMEM supplemented with 5 mM of glucose and 0.5% of FBS) for next 3-4 days to stimulate the formation of myotubes. Three hrs before the treatment with selected agents, cells were washed with PBS and transferred to PBS supplemented with 5mM of glucose.

Human skeletal muscle cells (HSKM) were cultured in SKBM-2 mediums provided by Clonetics. 48 hrs after cell plating, medium was changed to SKBM medium to stimulate differentiation of the cells to myotubes. When differentiated, the myotubes were transferred to PBS supplemented with 5mM glucose for three hrs before the treatment.

Analysis of C2C12 cells for the level of activated AMPK, Akt and the level of GLUT-4 was performed in the same experimental system. The cells were treated for 30 minutes at 37 °C. After the treatment, the cells were washed with ice-cold PBS and lysed with 80ul of lysis buffer/well (M-PER buffer from Pierce supplemented with protease and phosphatase inhibitor mix (Calbiochem) for 10 minutes on ice. Next, the plates were transferred to –20 °C to improve the lysis of the cells. Next cells were sonicated for 5 minutes and lysate was transferred to Eppendorf tubes and centrifuged at 14,000rpm for 10 minutes. Supernatants were collected in fresh Eppendorf tubes and kept on ice to measure the amount of total proteins. 3µl of each lysate was used to measure the protein concentration using standard Bradford method (Biorad). Subsequently, 20µg per sample of sample protein was used for Western analysis using NuPage 10% Bis/Tris gels (Invitrogen). After exposure of membranes to primary and secondary antibodies AMPK, AKT or Glut-4 was detected using ECL-Plus (Amersham) following producer's instruction. Chemilumiscent signals were detected by using ChemiDoc system from Biorad. Intensity of detected signals were analyzed and measured using Quantity One software (Biorad). Alternatively, the level of phosphorylated AMPK was detected using ECL kit from Amersham and short exposure to Kodak films.

Experimental setup:

1. Cell Culture
2. Treatment
3. Cell Lysis
4. Western blot analysis
    a. AMPK
    b. Akt
    c. GLUT4
    d. Total AMPK
    e. Total Akt
5. Signal measure

AMPK, AKT and GLUT-4 were measured from the same samples.

Primary antibodies used in these studies are the following:

1. Anti-phospho-AMPK (Thr172), mouse, rabbit IgG, from Cell Signaling, #2531
2. Anti-phospho-Akt (Ser473), mouse, rabbit IgG, Cell Signaling, #9271
3. Anti-Glut-4, mouse, rabbit IgG, Calbiochem, #400064
4. Anti-AMPK (total), mouse, rabbit IgG, Cell Signaling, #2532
5. Anti-Akt (total), mouse, rabbit IgG, Cell Signaling, #9272

The effects of various purine derivative, including cytokinins, on AMPK activity are summarized in Table 5. The results demonstrate that most of the tested agents potently stimulate AMPK activity, with some resulting in over 10 fold increases in activity compared the untreated control. The more potent compounds includes derivatives of adenine, cytidine and guanosine as well as kinetin and zeatin.

2 **Table 5 – Effects on AMPK in C2C12 muscle cells *in vitro***

Agent	Concentration		Experiment No.	Fold AMPK Activation (over control)
Adenosine	µM	12.5	11-2	1.83
		5.0		1.64
		2.5		1.87
N6-Acetyl-Adenosine	µM	12.5	11-2	2.18
		5.0		2.41
		2.5		1.08
Benzyl-Adenine	µM	50.0	7-2	2.92
		5.0		2.70
		0.5		2.18
Gamma, Gamma-Dimethylally-6-Aminopurine	µM	50.0	7-2	2.11
		5.0		2.45
		0.5		2.82
Dihydro-Zeatin	µM	50.0	6-2	0.88
		5.0		0.59
		0.5		2.25
Zeatin	µM	1.0	112802	2.33
		10.0	112702	2.04
		1.0		2.15
Trans-Zeatin	µM	10.0	112702	4.27
		1.0		2.33
Guanosine	µM	5.0	19-2	3.70
N2-Acetyl-Guanosine	µM	2.0	19-2	2.20
		0.8		2.20
		0.3	23-1	3.75
		1.5		4.28
		7.5		1.71
		37.5		2.28
N2-Acetyl-Guanine	µM	0.3	23-1	5.42
		1.5		5.85
		7.5		6.00
		37.5		6.51
Kinetin	µM	0.8	19-2	3.60
		0.8	20-1	2.40
		2.0		2.70
		10.0		12.80
		0.1	17-4	5.30
		0.3		8.12
		1.0		19.50
		3.0		14.50
Kinetin Riboside	µM	3.0	17-4	12.00
Metformin	mM	2.0	23-3	1.42
Rosiglitazone	µM	3.0	19-2	3.50

The effects of various purine derivative, including cytokinins, on Akt activity are summarized in Table 6. Many of the potent AMPK stimulators had only marginal effect on Akt activity. For example, zeatin is a potent stimulator of AMPK but not Akt. However, guanosine, N2-Acetyl-Guanosine and N2-Acetyl-Guanine were observed to be potent activators of AMPK as well as Akt.

Table 6 – Effects on Akt in C2C12 muscle cells *in vitro*

Agent	Concentration		Experiment No.	Fold Akt Activation (over control)
Kinetin	µM	5.0	14-6	2.07
		2.0		3.35
		0.8		3.17
		8.1	22-2	0.24
		2.7		3.21
		0.9		3.81
		0.3		5.08
Kinetin Riboside	µM	5.0	14-6	3.32
		2.0		5.14
		0.8		3.71
Zeatin	µM	10.0	271102	1.36
		1.0		0.95
Trans-Zeatin	µM	10.0	271102	0.86
		1.0		0.90
Gamma, Gamma-Dimethylally-6-Aminopurine	µM	2.0	14-4	1.32
		0.8		1.90
		0.8	14-6	3.56
N4-Acetyl-Cytidine	µM	5.0	12-3	1.64
		2.0		1.46
		0.8		2.45
		5.0	11-10	1.36
		2.0		1.50
N2-Acetyl-Guanosine	µM	5.0	17-1	1.23
		0.8		1.75
		0.3		1.92
		0.1		2.57
		2.0	19-2	2.17
		0.8		2.95
		7.5	23-1	1.68
		1.5		1.55
		0.3		2.57
N2-Acetyl-Guanine	µM	7.5	22-1	2.58
		1.5		3.58
		0.3		3.50
		7.5	23-1	1.95
		1.5		1.64
		0.3		2.44
AICAR	µM	500.0	17-6	5.45
		50.0		2.20
Metformin		mM	22-1	2.32
		20.0		2.70
		2.0		
Insulin	nM	100.0	14-3	1.75
		50.0		3.28
		25.0		3.40
Rosiglitazone	µM	27.0	22-2	0.71
		9.0		1.78
		3.0		2.34
		3.0	17-6	5.01
		1.0		2.83

The effects of kinetin, N2-Acetyl-Guanosine and N2-Acetyl-Guanine on GLUT-4 protein level in C2C12 cells were investigated following the same experimental design as described for AMPK and AKT. Anti-Glut-4 antibody used in this study was from Calbiochem. The results summarized in Table 7 demonstrate that kinetin, N2-Acetyl-Guanosine and N2-Acetyl-Guanine potently increase GLUT-4 protein level in C2C12 cells at different range and in a dose-dependent manner.

Table 7 – Effects on GLUT-4 in C2C12 muscle cells *in vitro*

Agent	Concentration		Experiment No.	Fold Change in GLUT-4 Level (over control)
Rosiglitazone	μM	3.0	22-2	3.82
		9.0		3.61
		27.0		3.19
		3.0	22-1	2.13
		3.0	19.2	4.37
		3.0	20-1	2.98
Metformin	mM	2.0	22-1	1.50
Kinetin	μM	0.3	22-2	3.45
		0.9		4.00
		2.7		3.88
		8.1		1.11
		0.8	19-2	3.46
		0.3	20-1	3.95
		0.8		2.36
		2.0		1.88
N2-Acetyl-Guanine	μM	0.3	22-2	3.94
		1.5		3.84
		7.5		3.24
		37.5		2.80
N2-Acetyl-Guanosine	μM	0.3	22-2	1.21
		1.5		1.74
		7.5		3.14
		37.5		3.03

Example 2

Total glucose uptake was measured using fluorescent glucose analog from Molecular Probes. Briefly, muscle cells were treated with kinetin, N2-Acetyl-Guanosine and N2-Acetyl-Guanine for 30 minutes at 37C first and subsequently, these cells were exposed to 500 μM of fluorescent glucose analog for 5 minutes at room temperature. Next, cells were washed twice with cold Krebs-Hepes buffered solution and fixed in 70% ethanol in water. Fluorescence of fluorescent glucose in the cells was measured using fluorescent plate reader at 480/530 nm (excitation/emission). The results summarized in Table 8 demonstrate that kinetin, N2-Acetyl-Guanosine and N2-Acetyl-Guanine each potently enhance glucose uptake in muscle cells *in vitro*.

Table 8 - Effects on Glucose Uptake in Muscle Cells *In Vitro*.

Agent	Concentration		Average Values (n=3)	Fold Change in Total Glucose Uptake (over control)
N2-Acetyl-Guanosine	µM	0.0	20.3 +/-0.1	-
		0.3	44.1 +/-0.7	2.17
		1.5	54,3 +/-0.9	2.67
		7.5	61.7 +/-1.3	3.03
		0.00	46.5 +/- 1.2	-
		0.15	90.5 +/- 1.7	1.94
		0.75	109.5 +/-2.6	2.35
		3.75	148.7 +/- 8.5	3.18
N2-Acetyl-Guanine	µM	0.3	54.5 +/- 1.7	2.68
		1.5	55.2 +/- 0.8	2.71
		7.5	59.6 +/-0.4	2.93
		0.00	46.5 +/-1.2	-
		0.15	86.4+/- 2.3	1.85
		3.75	115.9+/- 3.7	2.48
Kinetin	µM	0.00	47+/- 0.7	-
		0.15	88.6+/- 0.9	1.88
		0.75	103.3+/-2.1	2.19
		3.75	102.6+/-4.7	2.18
		0.0	28.9+/-0.1	-
		0.3	86.0+/-0.7	2.97
		1.5	110.6+/-2.3	3.82
		7.5	56.6+/-1.4	1.95
Rosiglitazone	µM	3.0	47.3 +/-1.1	2.33
		30.0	56.5 +/- 1.4	2.78
		0.0	52.1 +/-0.2	-
		3.0	122.4 +/-3.7	2.34

Example 3

The ability of a compound to increase the fermentation rate of yeast was evaluated as a potential initial screen for selected compounds having a desired biological activity. The fermentation rate of Saccharomyces cerevisiae was measured according to Warburg methodology by determination of evolved carbon dioxide during fermentation process.

Dry commercial Baker's Yeast used in all experiments. The fermentation medium comprised about 2.5% glucose in 63 mM phosphate buffer (pH 6.3). The effects of test substances on the rate yeast fermentation were compared with the rate yeast fermentation in control tests lacking the test substance.

Tests were conducted employing an apparatus comprising two parallel units for simultaneous fermentation rate measurement in presence of the tested substance (Probe) and in absence of it (Control). Units were identical consisting of the fermentation vessels (Erlenmeyer flask, 100 ml) connected to a manometric U tube (h =25 cm, diameter = 2 mm) equipped with valve and filled with light liquid such as isopropanol. Erlenmeyer flasks were equipped with magnetic stirring bars and placed on a magnetic stirrer (20-25 cm diameter). Generally, the amount of yeast employed was fixed at about 50 mg, while the volume of fermentation medium was generally about 20 mL. The amounts of tested substances varied from 0.020 mg to 0.700 mg, depending on their activities.

In a practical experiment both systems are simultaneously pre-incubated under aerobic conditions for 10 minutes (open valves). Fermentation process under anaerobic conditions and the real rate measurements start after closing the valves. The fermentation rates were monitored 5 minute interval for 50 minutes by observing the differences of the liquid heights in U-tubes (which differences correspond to a pressure difference between a

reaction vessel and an atmosphere - deltaP). The results summarized in Table 9 demonstrate that various of the contemplated compounds, including cis-zeatin, trans-zeatin, dihydro-zeatin, benzyl-adenine, gamma,gamma-dimethylallyl-6-aminopurine, kinetin riboside, N6-acetyl-adenosine, N2-acetyl-Guanosine, N4-acetyl-cytidine, enhance yeast fermentation rates.

Table 9 - Effects on Yeast Fermentation Rate

Tested substances	Concentration	Enhancement of Yeast Fermentation Rate (after 60 minutes; control=1)
Cis-Zeatin	6.2 µM	1.44
Trans-Zeatin	8.9 µM	1.17
Dihydro-Zeatin	9.1 µM	1.738
Benzyl-Adenine	11.3 µM	1.74
Gamma,gamma-dimethylallyl-6-aminopurine	21.3 µM	1.92
Kinetin Riboside	101 µM	1.67
N6-acetyl-Adenosine	30.7 µM	1.92
N2-acetyl-Guanosine	13.3 µM	1.98
N4-acetyl-Cytidine	15.1 µM	2.05
AICAR	135.5 µM (35 mg/L)	1.77

Example 4

Conditions and disorders associated with AMPK regulation of liver are among those treatable by administering a composition comprising a compound that activates AMPK. Acetyl-CoA carboxylase (ACC) and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) are two classical targets for the AMPK system, catalyzing the key regulatory steps in fatty

acid and sterol synthesis, respectively (Winder et al, Am J Physiol, 2777: E1-10, 1999, the entirety of which is herein incorporated by reference.) Activation of AMPK serves to inhibit both these lipid biosynthetic pathways, as well as triglyceride synthesis. Moreover, it is suggested that activated AMPK inhibits the L-type pyruvate kinase and fatty acid synthase gene expression. Inactivation of ACC in the liver cell also leads to decreases in the concentration of the product of ACC, i.e., malonyl-CoA, which has marked effects on fatty acid oxidation. Malonyl-CoA is a potent inhibitor of carnitine palmitoyltransferase-1 (CPT-1), the "gatekeeper" for entry of fatty acids into the mitochondria. In the liver, fatty acid oxidation can be considered to be an essential component of the pathway for synthesis of ketone bodies: increases in fatty acid oxidation lead to increased hepatic ketogenesis. Administering the composition to activate AMPK in the liver would result in decreases in fatty acid, triglyceride, and sterol synthesis and increases in fatty acid oxidation and ketogenesis. Thus, treatment with the composition to increase AMPK activity is useful in reducing fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression, and in ameliorating disorders that are characterized by elevations in one or more of these pathways or mechanisms, or that are exacerbated by the effects of one or more of these pathways or mechanisms, as would be recognized by one of skill in the art. Treatment with the composition to increase AMPK activity is also useful in increasing fatty acid oxidation and ketogenesis where increased ketogenesis is desired as would be recognized by one of skill in the art.

Example 5

Conditions and disorders associated with AMPK regulation of fat cell metabolism are among those treatable by administering a composition comprising a compound that activates AMPK. Hormone-sensitive lipase (HSL) is a target for AMPK in adipose tissue. (*Ibid.*) Activation of AMPK has been shown to inhibit lipogenesis by phosphorylation of ACC and also to inhibit isoprenaline-stimulated lipolysis. Thus, treatment with the composition to increase AMPK activity is useful in inhibiting lipogenesis and isoprenaline-stimulated lipolysis, and in ameliorating disorders that are characterized by elevations in one or both of these pathways, or that are exacerbated by the elevations in one or both of these pathways, as would be recognized by one of skill in the art.

Example 6

Conditions and disorders associated with AMPK regulation of insulin secretion are among those treatable by administering a composition comprising a compound that activates AMPK. Activated AMPK is thought to inhibit insulin secretion. (*Ibid.*) Since the contemplated compounds activate AMPK, treatment with the composition is useful in decreasing insulin secretion and in ameliorating disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion, as would be recognized by one of skill in the art.

Example 7

Conditions and disorders associated with AMPK regulation of muscle metabolism and glucose uptake are among those treatable by administering a composition comprising a

compound that activates AMPK. The effect of contraction on glucose uptake in muscle is well documented. It has been observed that either of exercise or electrical stimulation of muscle increases AMPK activity and also increases glucose uptake. It has also been observed that glucose uptake is increased by chemical activation of AMPK with AICA-riboside. Based on these observations, it has been hypothesized that muscle contraction plays a role in stimulating glucose uptake in muscle, where one mechanism underlying increased uptake stems from activated AMPK increasing GLUT-4 translocation from microvesicles to sarcolemmal membranes in muscle. (*Ibid.*) Thus, treatment with the composition to increase AMPK activity is useful in enhancing glucose uptake in muscle cells, and in ameliorating disorders that are characterized by decreased glucose uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle cells, as would be recognized by one of skill in the art.

Example 8

Conditions and disorders associated with AMPK regulation of cytoplasmic concentrations of HuR are among those treatable by administering a composition comprising a compound that activates AMPK. HuR is an RNA binding protein that functions to stabilize a variety of target mRNA transcripts, including those encoding p21, cyclinA and cyclinB1. It has been shown that the presence of activated AMPK results in reduced levels of cytoplasmic HuR, and in turn, in reduced concentrations and half-lives of mRNA encoding p21, cyclinA and cyclinB1. (Mol Cell Biol, 22(10):345-36, 20002, the entirety of which is herein incorporated by reference) Thus, treatment with the composition to increase AMPK activity is useful in reducing levels of cytoplasmic HuR, and in turn, in reducing

concentrations and half-lives of a variety of target mRNA transcripts, including but not limited to those encoding p21, cyclinA and cyclinB1, and in ameliorating disorders that are characterized decreased levels of HuR and its target transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target transcripts, as would be recognized by one of skill in the art.

Example 9

Conditions and disorders associated with AMPK regulation of glucocorticoid-induced apoptosis are among those treatable by administering a composition comprising a compound that activates AMPK. Activated AMPK has been shown to provide protection against glucocorticoid-induced apoptosis and to restore cell viability and inhibit DNA laddering in dexamethasone-treated thymocytes. (Biochem Biophys Res Commun, 243(3):821-6, 1998, the entirety of which is herein incorporated by reference) Furthermore, activated AMPK has been shown to provide protection against dexamethasone-induced activation of caspase 3-like enzymes, which are believed to play a pivotal role in apoptotic cell death. Thus, treatment with the composition to increase AMPK activity is useful in providing protection against glucocorticoid-induced apoptosis as would be recognized by one of skill in the art, and in ameliorating disorders that are characterized by increased glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced apoptosis, as would be recognized by one of skill in the art.

Example 10

Conditions and disorders associated with AMPK regulation of cellular responses to stresses, including ischemia, are among those treatable by administering a composition comprising a compound that activates AMPK. In several non-vascular tissues in which it has been studied, AMPK appears to modulate the cellular response to stresses such as ischemia. In liver and muscle, AMPK phosphorylates and inhibits acetyl CoA carboxylase (ACC), leading to an increase in fatty acid oxidation; and in muscle, its activation is associated with an increase in glucose transport. Furthermore, incubation of human umbilical vein endothelial cells (HUVEC) with an AMPK activator has been shown to cause a 5-fold activation of AMPK, which was accompanied by a 70% decrease in ACC activity and a 2-fold increase in fatty acid oxidation. (Biochem Biophys Res Commun, 265(1):112-5, 1999, the entirety of which is herein incorporated by reference) However, in this same study, glucose uptake and glycolysis, the dominant energy-producing pathway in HUVEC, were diminished by 40-60% under these conditions. Despite this, cellular ATP levels were increased by 35%. Thus, treatment with the composition to increase AMPK activity is expected to result in major alterations in endothelial cell energy balance, which are useful in providing protection against cellular stresses in conditions including ischemia, as would be recognized by one of skill in the art.

Example 11

Conditions and disorders associated with adipogenesis are among those treatable by administering a composition comprising a compound that activates AMPK. The AMPK activator, 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), has been found to

inhibit the differentiation of 3T3-L1 adipocytes, if added at an early phase of differentiation. (Biochem Biophys Res Commun, 286(5):852-6, the entirety of which is herein incorporated by reference). AICAR blocks the expression of the late adipogenic markers, fatty acid synthase and acetyl-CoA carboxylase, and of the transcription factors, C/EBPalpha and PPARgamma. It also inhibits early clonal expansion of pre-adipocytes, prevents the fall in C/EBPbeta expression during the intermediate stage of differentiation and inhibits the late phase expression of CHOP-10, an antagonist of C/EBPbeta. Thus, given the inhibitory role for AMPK in the process of adipose differentiation, treatment with the composition to increase AMPK activity is useful in inhibiting adipogenesis as would be recognized by one of skill in the art, and in ameliorating conditions and disorders that are characterized by increased adipogenesis, or that are exacerbated by adipogenesis, as would be recognized by one of skill in the art.

Example 12

Conditions and disorders associated with metabolic and excitotoxic insults relevant to the pathogenesis of several different neurodegenerative conditions are among those treatable by administering a composition comprising a compound that activates AMPK. It is well known that the brain has a high metabolic rate and is sensitive to changes in the supply of glucose and oxygen. The expression of AMPK in embryonic and adult brain and its role in modifying neuronal survival under conditions of cellular stress have been investigated. (J Mol Neurosci, 17(1): 45-58, 2001, the entirety of which is herein incorporated by reference) Catalytic (alpha1 and alpha2) and noncatalytic (beta2 and gamma1) subunits of AMPK are present at high levels in embryonic hippocampal neurons in vivo and in cell culture. In the

adult brain, the catalytic subunits alpha1 and alpha2 are present in neurons throughout the brain. The AMPK-activating agent AICAR protected hippocampal neurons against death induced by glucose deprivation, chemical hypoxia, and exposure to glutamate and amyloid beta-peptide. Suppression of levels of the AMPK alpha1 and alpha2 subunits using antisense technology resulted in enhanced neuronal death following glucose deprivation, and abolished the neuroprotective effect of AICAR. Thus, given the role of AMPK activation in modifying neuronal survival under conditions of cellular stress, treatment with the composition to increase AMPK activity is useful in protecting neurons against metabolic and excitotoxic insults relevant to the pathogenesis of several different neurodegenerative conditions as would be recognized by one of skill in the art.

Example 13

Conditions and disorders associated with hypoxia are among those treatable by administering a composition comprising a compound that activates AMPK. AMPK is believed to play a role in regulating ketone body production by astrocytes. (J Neurochem, 73(4): 1674-82, 1999, the entirety of which is herein incorporated by reference). Incubation of astrocytes with AICAR has been shown to stimulate both ketogenesis from palmitate and carnitine palmitoyltransferase I concomitant to a decrease of intracellular malonyl-CoA levels and an inhibition of acetyl-CoA carboxylase/fatty acid synthesis and 3-hydroxy-3-methylglutaryl-CoA reductase/cholesterol synthesis. Moreover, microdialysis experiments have shown AICAR to stimulate brain ketogenesis markedly. Incubation of astrocytes with azide has been shown to lead to a remarkable drop of fatty acid beta-oxidation. However, activation of AMPK during hypoxia was shown to compensate the depression of beta-

oxidation, thereby sustaining ketone body production. The effect is believed to rely on the following cascade: hypoxia => increase of the AMP/ATP ratio => AMPK stimulation => acetyl-CoA carboxylase inhibition => decrease of malonyl-CoA concentration => carnitine palmitoyltransferase I deinhibition => enhanced ketogenesis. Furthermore, incubation of neurons with azide has been shown to blunt lactate oxidation, but not 3-hydroxybutyrate oxidation. Thus, given the role of AMPK activation in regulating ketone body production by astrocytes, treatment with the composition to increase AMPK activity is useful in promoting astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism during hypoxia.

Example 14

Conditions and disorders associated with diminished insulin sensitivity of muscle glucose transport are treatable by administering a composition comprising a compound that activates AMPK. A study to determine the degree to which hypoxia and AICAR, which also activate AMPK and stimulate glucose transport, also induce an increase in insulin sensitivity has been reported. (Am J Physiol Endocrinol Metab, 282(1): E18-23, 2002, the entirety of which is herein incorporated by reference) The study found that the increase in glucose transport in response to 30 microU/ml insulin was about two-fold greater in rat epitrochlearis muscles that had been made hypoxic or treated with AICAR 3.5 h previously than in untreated control muscles. This increase in insulin sensitivity was similar to that induced by a 2-h bout of swimming or 10 min of in vitro electrically stimulated contractions. Neither phosphatidylinositol 3-kinase activity nor protein kinase B (PKB) phosphorylation in response to 30 microU/ml insulin was enhanced by prior exercise or AICAR treatment

that increased insulin sensitivity of glucose transport. Inhibition of protein synthesis by inclusion of cycloheximide in the incubation medium for 3.5 h after exercise did not prevent the increase in insulin sensitivity. Contractions, hypoxia, and treatment with AICAR all caused a two- to three-fold increase in AMPK activity over the resting level. These results provide evidence that the increase in insulin sensitivity of muscle glucose transport that follows exercise is mediated by activation of AMPK. Thus, treatment with the composition to increase AMPK activity is useful in increasing insulin sensitivity of muscle glucose transport.

Example 15

Occurrences of hepatic ischemia-reperfusion (I/R) injury associated with liver transplantation and hepatic resections can be reduced by administering a composition comprising a compound that activates AMPK. Preconditioning is known to preserve energy metabolism in liver during sustained ischemia. A study has been reported that investigates: 1) whether preconditioning induces AMPK activation; and 2) if AMPK activation leads to ATP preservation and reduced lactate accumulation during prolonged ischemia and its relationship with NO. (Hepatology, 34(6): 1164-73, 2001, the entirety of which is herein incorporated by reference) Preconditioning was reported to activate AMPK and concomitantly reduce ATP degradation, lactate accumulation, and hepatic injury. The administration of an AMPK activator, AICAR, before ischemia simulated the benefits of preconditioning on energy metabolism and hepatic injury. The inhibition of AMPK abolished the protective effects of preconditioning. The effect of AMPK on energy metabolism was independent of NO because the inhibition of NO synthesis in the

preconditioned group and the administration of the NO donor before ischemia, or to the preconditioned group with previous inhibition of AMPK, had no effect on energy metabolism. Thus, given the role of AMPK activation in the protective effect against ischemia, treatment with the composition to increase AMPK activity is useful in surgical and pharmacological strategies aimed at reducing hepatic I/R injury.

Example 16

Conditions and disorders associated with hyperglycemia are treatable by administering a composition comprising a compound that activates AMPK. It has recently been reported that therapeutic doses of metformin increase AMPK activity in vivo in subjects with type 2 diabetes. (Diabetes, 51(7): 2074-81, 2002, the entirety of which is herein incorporated by reference) Metformin treatment for 10 weeks significantly increased AMPK alpha2 activity in the skeletal muscle, and this was associated with increased phosphorylation of AMPK on Thr172 and decreased acetyl-CoA carboxylase-2 activity. The increase in AMPK alpha2 activity was likely due to a change in muscle energy status because ATP and phosphocreatine concentrations were lower after metformin treatment. Metformin-induced increases in AMPK activity were associated with higher rates of glucose disposal and muscle glycogen concentrations. These findings suggest that the metabolic effects of metformin in subjects with type 2 diabetes may be mediated by the activation of AMPK alpha2. Given the hypoglycemic effect imparted by the activation of AMPK, treatment with the composition to increase AMPK activity is useful to lower blood glucose concentrations by decreasing hepatic glucose production and increasing glucose disposal in skeletal muscle.

Example 17

Conditions and disorders associated with insulin resistance syndrome are treatable by administering a composition comprising a compound that activates AMPK. Insulin resistance syndrome is associated with obesity, type 2 diabetes, and muscle paralysis. (WO 01/97816 A1 and WO 01/93874 A1, the entireties of which are herein incorporated by reference.) Insulin resistance syndrome is also associated with several risk factors for cardiovascular disease. Chronic chemical activation of AMP-activated protein kinase by the adenosine analog AICAR has been shown to augment insulin action, upregulate mitochondrial enzymes in skeletal muscles, and decrease the content of intra-abdominal fat, including that occurring in obesity. (WO 01/93873 A1, the entirety of which is herein incorporated by reference.) Furthermore, acute AICAR exposure has been found to reduce sterol and fatty acid synthesis in rat hepatocytes incubated in vitro as well as suppress endogenous glucose production in rats under euglycemic clamp conditions. A recent study investigated whether chronic AICAR administration, in addition to the beneficial effects on insulin sensitivity in type 2 diabetes, is capable of improving other phenotypes associated with the insulin resistance syndrome. (Diabetes, 51(7): 2199-206, 2002, the entirety of which is herein incorporated by reference) AICAR administration significantly reduced plasma triglyceride levels ($P < 0.01$ for AICAR vs. AL, and $P = 0.05$ for AICAR vs. PF) and free fatty acids ($P < 0.01$ for AICAR vs. AL, and $P < 0.05$ for AICAR vs. PF) and increased HDL cholesterol levels ($P < 0.01$ for AICAR vs. AL and PF). AICAR treatment also lowered systolic blood pressure by 14.6 +/- 4.3 mmHg ($P < 0.05$), and AICAR-treated animals exhibited a tendency toward decreased intra-abdominal fat content. Furthermore,

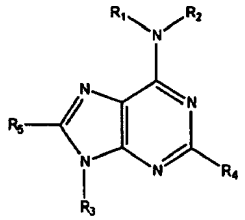
AICAR administration normalized the oral glucose tolerance test and decreased fasting concentrations of glucose and insulin close to the level of the lean animals. Finally, in line with previous findings, AICAR treatment was also found to enhance GLUT4 protein expression and to increase maximally insulin-stimulated glucose transport in primarily white fast-twitch muscles. In view of the strong evidence that activating AMPK improves glucose tolerance, improves the lipid profile, and reduces systolic blood pressure, treatment with the composition to increase AMPK activity is useful to reduce metabolic disturbances and lowers blood pressure characteristic of insulin resistance syndrome.

While a number of embodiments of this invention have been herein before described, it is apparent that the basic embodiments can be altered to provide other embodiments of the disclosed invention. Therefore, it will be appreciated that the scope of this invention includes all alternative embodiments and variations which are described in the foregoing specification and by the claims appended hereto. The invention is not to be limited by the specific embodiments that have been presented herein by way of example.

CLAIMS

We claim:

1. A pharmaceutical composition comprising a unit dosage of a cytokinin having the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl, alkenyl or alkynyl.

2. The pharmaceutical composition of claim 1, wherein the cytokinin is selected from one or more of: dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of claim 2, wherein the cytokinin is selected from one or more of: dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside; and/or a hydrate, solvate, tautomer, and/or pharmaceutically acceptable salt thereof.

4. The pharmaceutical composition of claim 1, wherein the cytokinin is selected from one or more of: a naturally occurring cytokinin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

5. The pharmaceutical composition of claim 1, wherein the cytokinin is selected from one or more of: a non-naturally occurring cytokinin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

6. The pharmaceutical composition of claim 1, wherein the cytokinin is selected from one or more of: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-

zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

7. The pharmaceutical composition of claim 6, wherein the unit dosage comprises one or more of: N6-gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

8. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: N6-gamma, gamma-dimethyl-allyl-aminopurine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

9. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: dihydro-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

10. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: cis-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

11. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: trans-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

12. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: N6-isopentenyl-adenine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

13. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: N6-isopentenyl-adenosine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

14. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: N6-benzyl-adenine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

15. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: N6-benzyl-adenosine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

16. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: kinetin (6-furfurylaminpurine), and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

17. The pharmaceutical composition of claim 7, wherein the unit dosage comprises one or more of: kinetin riboside, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a unit dosage of one or more of: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-

isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

19. The pharmaceutical composition of claim 18, wherein the unit dosage comprises one or more of: N6-gamma, gamma-dimethyl-allyl-aminopurine, dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

20. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: N6-gamma, gamma-dimethyl-allyl-aminopurine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

21. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: dihydro-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

22. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: cis-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

23. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: trans-zeatin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

24. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: N6-isopentenyl-adenine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

25. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: N6-isopentenyl-adenosine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

26. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: N6-benzyl-adenine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

27. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: N6-benzyl-adenosine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

28. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: kinetin (6-furfurylaminpurine), and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

29. The pharmaceutical composition of claim 19, wherein the unit dosage comprises one or more of: kinetin riboside, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

30. The pharmaceutical composition of any one of claims 1-29, wherein the unit dosage comprises a cytokinin, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, in an amount sufficient to increase, following oral or parenteral administration of said unit dosage to a patient in need thereof, an intracellular level of activated AMPK and/or an intracellular level of activated Akt in one or more cell types and/or tissue types of said patient.

31. The pharmaceutical composition of claim 30, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 20% over pre-administration levels.

32. The pharmaceutical composition of claim 31, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 30% over pre-administration levels.

33. The pharmaceutical composition of claim 32, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of

activated Akt in one or more cell types and/or tissue types of said patient by at least 50% over pre-administration levels.

34. The pharmaceutical composition of claim 33, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 75% over pre-administration levels.

35. The pharmaceutical composition of claim 34, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least two-fold over pre-administration levels.

36. The pharmaceutical composition of claim 35, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least four-fold over pre-administration levels.

37. The pharmaceutical composition of claim 36, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least ten-fold over pre-administration levels.

38. The pharmaceutical composition of any one of claims 30-37, wherein the one or more cell types and/or tissue types include one or more of: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.

39. The pharmaceutical composition of any one of claims 30-37, wherein the one or more cell types and/or tissue types include myocytes.

40. The pharmaceutical composition of any one of claims 1-39 wherein the pharmaceutical composition is in a form suitable for oral ingestion.

41. The pharmaceutical composition of claim 40, wherein the form suitable for oral ingestion is one or more of a pill, capsule, tablet, cachet or lozenge.

42. The pharmaceutical composition of any one of claims 1-39, wherein the pharmaceutical composition is in a form suitable for parenteral injection.

43. The pharmaceutical composition of any one of claims 1-42, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

44. The pharmaceutical composition of any one of claims 1-43, wherein the pharmaceutical composition further comprises an additional therapeutic ingredient.

45. The pharmaceutical composition of claim 44, wherein the additional therapeutic ingredient is an anti-diabetic agent.

46. The pharmaceutical composition of claim 45, wherein the additional therapeutic ingredient is metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound, or a combination of any two or more thereof.

47. The pharmaceutical composition of claim 46, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.

48. The pharmaceutical composition of any one of claims 1-47, wherein the one or more cytokinins comprise, in total, at least 1%, by weight, of the pharmaceutical composition.

49. The pharmaceutical composition of claim 48, wherein one or more cytokinins comprise, in total, at least 2%, 3%, 4%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99%, by weight, of the pharmaceutical composition.

50. The pharmaceutical composition of any one of claims 1-49, wherein the pharmaceutical composition is a substantially pure pharmaceutical composition.

51. The pharmaceutical composition of any one of claims 1-50, wherein the pharmaceutical composition consists essentially of a cytokinin and a pharmaceutical carrier.

52. The pharmaceutical composition of any one of claims 1-51, comprising one or more cytokinins purified from a plant or yeast extract.

53. The pharmaceutical composition of any one of claims 1-51, consisting essentially of:

(a) one or more of: dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier; and optionally

(c) one or more additional agents to treat diabetes.

54. The pharmaceutical composition of any one of claims 1-51, consisting essentially of:

(a) one or more of: dihydro-zeatin, cis-zeatin, trans-zeatin, N6-isopentenyl-adenine, N6-isopentenyl-adenosine, N6-benzyl-adenine, N6-benzyl-

adenosine, kinetin (6-furfurylaminpurine) and kinetin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier.

55. A method for treating or preventing diabetes comprising administering to a human or other animal an effective dosage of the pharmaceutical composition of any one of claims 1-54.

56. A method of decreasing blood glucose level comprising administering to a human or other animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-54.

57. A method of treating impaired glucose tolerance comprising administering to a human or animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-54.

58. The method according to any of claims 55, 56 and 57, wherein said pharmaceutical composition is administered in a dosage amount of from 0.001 mg/kg/day to 100 mg/kg/day.

59. The method according to claim 58 wherein the dosage amount is 0.1 mg/kg/day to 50 mg/kg/day.

60. A method of treating or preventing diabetes comprising administering to a human or other animal an effective dosage of i) the pharmaceutical composition of any one of claims 1-54 in association with ii) one or more other agents chosen from: an agent or agents to treat diabetes, glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, glucosidase inhibitors and aldose reductase inhibitors.

61. The method of claim 60, wherein the agent or agents to treat diabetes include one or more of metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound.

62. The method of claim 61, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.

63. The method of claim 60, wherein the ingredients i) and ii) are simultaneously, separately, or sequentially administered.

64. A method for prophylaxis or treatment of a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity, said method comprising: providing a patient suffering from or believed to be at risk of

suffering from a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity; and administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-54.

65. The method of claim 64, wherein said disease or condition is a vascular disease associated with metabolic abnormalities.

66. The method of claim 65, wherein said disease or condition is atherosclerotic vascular disease.

67. The method of claim 64, wherein said disease or condition is selected from the group consisting of blindness, retinopathy and nephropathy caused by diabetic microvascular disease.

68. A method for activating adenosine 5'-monophosphate-activated protein kinase (AMPK) and/or Akt in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-54.

69. The method of claim 68, wherein the patient suffers from obesity.

70. The method of claim 68, wherein the patient suffers from insulin resistance.

71. The method of claim 68, wherein the patient suffers from a condition or disorder selected from the group consisting of: non-insulin dependent (type 2) diabetes mellitus, high blood pressure, elevated levels of triglycerides, hyperinsulinemia, glucose intolerance, low levels of high density lipoprotein (HDL), ischemia, hypoxia and glucocorticoid-induced apoptosis.

72. The method of claim 68, wherein the method results in one or more of the following:

(1) reduces one or more of fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;

(2) ameliorates one or more conditions or disorders that are characterized by elevations in one or more of the pathways or mechanisms involved in fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;

(3) increases fatty acid oxidation and ketogenesis;

(4) inhibits lipogenesis and/or isoprenaline-stimulated lipolysis;

(5) ameliorates one or more conditions or disorders that are characterized by elevations in one or both of lipogenesis and isoprenaline-stimulated lipolysis pathways, or that are exacerbated by the elevations in one or both of these pathways;

(6) decreases insulin secretion;

(7) ameliorates one or more a conditions or disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion;

(8) enhances glucose uptake in muscle cells;

(9) ameliorates one or more conditions or disorders that are characterized by decreased glucose uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle cells;

(10) reduces levels of cytoplasmic HuR, which in turn, reduces concentrations and half-lives of target mRNA transcripts;

(11) ameliorates one or more conditions or disorders that are characterized by decreased levels of HuR and its target transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target transcripts;

(12) provides protection against glucocorticoid-induced apoptosis;

(13) ameliorates one or more conditions or disorders that are characterized by increased glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced apoptosis;

(14) protects against cellular stresses resulting from ischemia;

(15) inhibits adipogenesis;

(16) ameliorates one or more conditions or disorders that are characterized by increased adipogenesis, or that are exacerbated by adipogenesis;

(17) protects neurons against metabolic and excitotoxic insults associated with the pathogenesis of a neurodegenerative condition;

(18) promotes astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism;

(19) increases insulin sensitivity of muscle glucose transport;

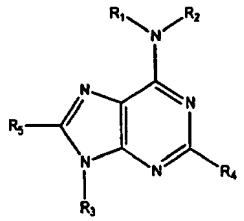
(20) protects against hepatic ischemia-reperfusion (I/R) injury associated with liver transplantation and hepatic resections;

(21) lowers blood glucose concentrations by decreasing hepatic glucose production and/or increasing glucose disposal in skeletal muscle; and

(22) ameliorates one or more conditions or disorders associated with insulin resistance syndrome through improving glucose tolerance, improving lipid profile or reducing systolic blood pressure.

73. The method of any one of claims 55-72, wherein said pharmaceutical composition is administered to said patient over a period of time of at least 28 days.

74. A pharmaceutical composition comprising a unit dosage of an adenine derivative having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

75. The pharmaceutical composition of claim 74, wherein the adenine derivative is selected from one or more of: an acyl-adenosine and an acyl-adenine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

76. The pharmaceutical composition of claim 75, wherein the adenine derivative is selected from one or more of: a mono-acyl-adenosine and a mono-acyl-adenine; and/or a hydrate, solvate, tautomer, and/or pharmaceutically acceptable salt thereof.

77. The pharmaceutical composition of claim 74, wherein the adenine derivative is selected from one or more of: an N6-acyl-adenine and an N6-acyl-adenosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

78. The pharmaceutical composition of claim 77, wherein the adenine derivative is selected from one or more of: N6-acetyl-adenine and N6-acetyl-adenosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

79. The pharmaceutical composition of claim 78, wherein the adenine derivative is selected from one or more of: a naturally occurring N6-acetyl-adenine and a naturally occurring N6-acetyl-adenosine, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

80. The pharmaceutical composition of claim 74, wherein the adenine derivative is selected from one or more of: a non-naturally occurring adenine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

81. The pharmaceutical composition of any one of claims 74-80, wherein the unit dosage comprises adenine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, in an amount sufficient to increase, following oral or parenteral administration of said unit dosage to a patient in need thereof, an intracellular level of activated AMPK and/or an intracellular level of activated Akt in one or more cell types and/or tissue types of said patient.

82. The pharmaceutical composition of claim 81, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of

activated Akt in one or more cell types and/or tissue types of said patient by at least 20% over pre-administration levels.

83. The pharmaceutical composition of claim 82, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 30% over pre-administration levels.

84. The pharmaceutical composition of claim 83, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 50% over pre-administration levels.

85. The pharmaceutical composition of claim 84, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least 75% over pre-administration levels.

86. The pharmaceutical composition of claim 85, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least two-fold over pre-administration levels.

87. The pharmaceutical composition of claim 86, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least four-fold over pre-administration levels.

88. The pharmaceutical composition of claim 87, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least ten-fold over pre-administration levels.

89. The pharmaceutical composition of any one of claims 81-88, wherein the one or more cell types and/or tissue types include one or more of: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.

90. The method of any one of claims 81-88, wherein the one or more cell types and/or tissue types include myocytes.

91. The pharmaceutical composition of any one of claims 74-90 wherein the pharmaceutical composition is in a form suitable for oral ingestion.

92. The pharmaceutical composition of claim 91, wherein the form suitable for oral ingestion is one or more of a pill, capsule, tablet, cachet or lozenge.

93. The pharmaceutical composition of any one of claims 74-90, wherein the pharmaceutical composition is in a form suitable parenteral injection.

94. The pharmaceutical composition of any one of claims 74-93, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

95. The pharmaceutical composition of any one of claims 74-94, wherein the pharmaceutical composition further comprises an additional therapeutic ingredient.

96. The pharmaceutical composition of claim 95, wherein the additional therapeutic ingredient is an anti-diabetic agent.

97. The pharmaceutical composition of claim 96, wherein the additional therapeutic ingredient is metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound, or a combination of any two or more thereof.

98. The pharmaceutical composition of claim 97, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.

99. The pharmaceutical composition of any one of claims 74-98, wherein one or more adenine derivatives comprise, in total, at least at least 1%, by weight, of the pharmaceutical composition.

100. The pharmaceutical composition of claim 99, wherein one or more adenine derivatives comprise, in total, at least 2%, 3%, 4%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99%, by weight, of the pharmaceutical composition.

101. The pharmaceutical composition of any one of claims 74-100, wherein the pharmaceutical composition is a substantially pure pharmaceutical composition.

102. The pharmaceutical composition of any one of claims 74-101, wherein the pharmaceutical composition consists essentially of an adenine derivative and a pharmaceutical carrier.

103. The pharmaceutical composition of any one of claims 74-102, comprising one or more adenine derivatives purified from a plant or yeast extract.

104. The pharmaceutical composition of any one of claims 74-103, consisting essentially of:

(a) one or more of: an adenine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier; and optionally

(c) one or more additional agents to treat diabetes.

105. The pharmaceutical composition of any one of claims 74-104, consisting essentially of:

(a) one or more of: an adenine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier.

106. A method for treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of the pharmaceutical composition of any one of claims 74-105.

107. A method of decreasing blood glucose level comprising the step of administering to a human or other animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 74-105.

108. A method of treating impaired glucose tolerance comprising the step of administering to a human or animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 74-105.

109. The method according to any of claims 106, 107 and 108, wherein said pharmaceutical composition is administered in a dosage amount of from 0.001 mg/kg/day to 100 mg/kg/day.

110. The method according to claim 109 wherein the dosage amount is 0.1 mg/kg/day to 50 mg/kg/day.

111. A method of treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of i) the pharmaceutical composition of any one of claims 74-105 in association with ii) one or more other agents chosen from: an agent or agents to treat diabetes, glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, glucosidase inhibitors and aldose reductase inhibitors.

112. The method of claim 111, wherein the agent or agents to treat diabetes include one of more of metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound.

113. The method of claim 112, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.

114. The method of claim 111, wherein the ingredients i) and ii) are simultaneously, separately, or sequentially administered.

115. A method for prophylaxis or treatment of a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity, said method comprising the steps of: providing a patient suffering from or believed to be at risk of suffering from a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity; and administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 74-105.

116. The method of claim 115, wherein said disease or condition is a vascular disease associated with metabolic abnormalities.

117. The method of claim 116, wherein said disease or condition is atherosclerotic vascular disease.

118. The method of claim 115, wherein said disease or condition is selected from the group consisting of blindness, retinopathy and nephropathy caused by diabetic microvascular disease.

119. A method for activating adenosine 5'-monophosphate-activated protein kinase (AMPK) and/or Akt in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 74-105.

120. The method of claim 119, wherein the patient suffers from obesity.

121. The method of claim 119, wherein the patient suffers from insulin resistance.

122. The method of claim 119, wherein the patient suffers from a condition or disorder selected from the group consisting of: non-insulin dependent (type 2) diabetes mellitus, high blood pressure, elevated levels of triglycerides, hyperinsulinemia, glucose intolerance, low levels of high density lipoprotein (HDL), ischemia, hypoxia and glucocorticoid-induced apoptosis.

123. The method of claim 119, wherein the method results in one or more of the following:

(1) reduces one or more of fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;

(2) ameliorates one or more conditions or disorders that are characterized by elevations in one or more of the pathways or mechanisms involved in fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;

(3) increases fatty acid oxidation and ketogenesis;

(4) inhibits lipogenesis and/or isoprenaline-stimulated lipolysis;

(5) ameliorates one or more conditions or disorders that are characterized by elevations in one or both of lipogenesis and isoprenaline-stimulated lipolysis pathways, or that are exacerbated by the elevations in one or both of these pathways;

(6) decreases insulin secretion;

(7) ameliorates one or more a conditions or disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion;

(8) enhances glucose uptake in muscle cells;

(9) ameliorates one or more conditions or disorders that are characterized by decreased glucose uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle cells;

(10) reduces levels of cytoplasmic HuR, which in turn, in reduces concentrations and half-lives of target mRNA transcripts;

(11) ameliorates one or more conditions or disorders that are characterized decreased levels of HuR and its target transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target transcripts;

(12) provides protection against glucocorticoid-induced apoptosis;

(13) ameliorates one or more conditions or disorders that are characterized by increased glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced apoptosis;

(14) protects against cellular stresses resulting from ischemia;

(15) inhibits adipogenesis;

(16) ameliorates one or more conditions or disorders that are characterized by increased adipogenesis, or that are exacerbated by adipogenesis;

(17) protects neurons against metabolic and excitotoxic insults associated with the pathogenesis of a neurodegenerative condition;

(18) promotes astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism;

(19) increases insulin sensitivity of muscle glucose transport;

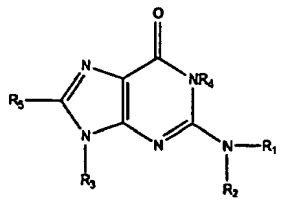
(20) protects against hepatic ischemia-reperfusion (I/R) injury associated with liver transplantation and hepatic resections;

(21) lowers blood glucose concentrations by decreasing hepatic glucose production and/or increasing glucose disposal in skeletal muscle; and

(22) ameliorates one or more conditions or disorders associated with insulin resistance syndrome through improving glucose tolerance, improving lipid profile or reducing systolic blood pressure.

124. The method of any one of claims 106-123, wherein said pharmaceutical composition is administered to said patient over a period of time of at least 28 days.

125. A pharmaceutical composition comprising a unit dosage of a guanine derivative having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

126. The pharmaceutical composition of claim 125, wherein the unit dosage comprises one or more of: an acyl-guanosine and an acyl-guanine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

127. The pharmaceutical composition of claim 126, wherein the unit dosage comprises one or more of: a mono-acyl-guanosine and a mono-acyl-guanine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

128. The pharmaceutical composition of claim 125, wherein the unit dosage comprises one or more of: an N6-acyl-guanine and an N6-acyl-guanosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

129. The pharmaceutical composition of claim 128, wherein the unit dosage comprises one or more of: N6-acetyl-guanine and N6-acetyl-guanosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

130. The pharmaceutical composition of claim 125, wherein the unit dosage comprises one or more of: a naturally occurring guanine derivative, and/or a racemate,

enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

131. The pharmaceutical composition of claim 125, wherein the unit dosage comprises one or more of: a non-naturally occurring guanine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

132. The pharmaceutical composition of any one of claims 125-131, wherein the unit dosage comprises guanine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, in an amount sufficient to increase, following oral or parenteral administration of said unit dosage to a patient in need thereof, an intracellular level of activated AMPK and/or an intracellular level of activated Akt in one or more cell types and/or tissue types of said patient.

133. The pharmaceutical composition of claim 132, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least two-fold.

134. The pharmaceutical composition of claim 133, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least four-fold.

135. The pharmaceutical composition of claim 134, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least ten-fold.

136. The pharmaceutical composition of any one of claims 132-135, wherein the one or more cell types and/or tissue types include one or more of: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.

137. The method of any one of claims 132-135, wherein the one or more cell types and/or tissue types include myocytes.

138. The pharmaceutical composition of any one of claims 125-137, wherein the pharmaceutical composition is in a form suitable for oral ingestion.

139. The pharmaceutical composition of claim 138, wherein the form suitable for oral ingestion is one or more of a pill, capsule, tablet, cachet or lozenge.

140. The pharmaceutical composition of any one of claims 125-137, wherein the pharmaceutical composition is in a form suitable parenteral injection.

141. The pharmaceutical composition of any one of claims 125-140, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

142. The pharmaceutical composition of any one of claims 125-141, wherein the pharmaceutical composition further comprises an additional therapeutic ingredient.

143. The pharmaceutical composition of claim 142, wherein the additional therapeutic ingredient is an anti-diabetic agent.

144. The pharmaceutical composition of claim 143, wherein the additional therapeutic ingredient is metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound, or a combination of any two or more thereof.

145. The pharmaceutical composition of claim 144, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.

146. The pharmaceutical composition of any one of claims 125-145, wherein one or more guanine derivatives comprise, in total, at least at least 1%, by weight, of the pharmaceutical composition.

147. The pharmaceutical composition of claim 146, wherein one or more guanine derivatives comprise, in total, at least 2%, 3%, 4%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99%, by weight, of the pharmaceutical composition.

148. The pharmaceutical composition of any one of claims 125-147, wherein the pharmaceutical composition is a substantially pure pharmaceutical composition.

149. The pharmaceutical composition of any one of claims 125-148, wherein the pharmaceutical composition consists essentially of a guanine derivative and a pharmaceutical carrier.

150. The pharmaceutical composition of any one of claims 125-149, comprising one or more guanine derivatives purified from a plant or yeast extract.

151. The pharmaceutical composition of any one of claims 125-150, consisting essentially of:

(a) one or more of: a guanine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier; and optionally

(c) one or more additional agents to treat diabetes.

152. The pharmaceutical composition of any one of claims 125-151, consisting essentially of:

(a) one or more of: a guanine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier.

153. A method for treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of the pharmaceutical composition of any one of claims 125-152.

154. A method of decreasing blood glucose level comprising the step of administering to a human or other animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 125-152.

155. A method of treating impaired glucose tolerance comprising the step of administering to a human or animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 125-152.

156. The method according to any of claims 153, 154 and 155, wherein said pharmaceutical composition is administered in a dosage amount of from 0.001 mg/kg/day to 100 mg/kg/day.

157. The method according to claim 156 wherein the dosage amount is 0.1 mg/kg/day to 50 mg/kg/day.

158. A method of treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of i) the pharmaceutical composition of any one of claims 125-152 in association with ii) one or more other agents chosen from: an agent or agents to treat diabetes, glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, glucosidase inhibitors and aldose reductase inhibitors.

159. The method of claim 158, wherein the agent or agents to treat diabetes include one of more of metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound.

160. The method of claim 159, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.

161. The method of claim 158, wherein the ingredients i) and ii) are simultaneously, separately, or sequentially administered.

162. A method for prophylaxis or treatment of a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity, said method comprising the steps of: providing a patient suffering from or believed to be at risk of suffering from a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity; and administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 125-152.

163. The method of claim 162, wherein said disease or condition is a vascular disease associated with metabolic abnormalities.

164. The method of claim 163, wherein said disease or condition is atherosclerotic vascular disease.

165. The method of claim 162, wherein said disease or condition is selected from the group consisting of blindness, retinopathy and nephropathy caused by diabetic microvascular disease.

166. A method for activating adenosine 5'-monophosphate-activated protein kinase (AMPK) and/or Akt in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 125-152.

167. The method of claim 166, wherein the patient suffers from obesity.

168. The method of claim 166, wherein the patient suffers from insulin resistance.

169. The method of claim 166, wherein the patient suffers from a condition or disorder selected from the group consisting of: non-insulin dependent (type 2) diabetes mellitus, high blood pressure, elevated levels of triglycerides, hyperinsulinemia, glucose intolerance, low levels of high density lipoprotein (HDL), ischemia, hypoxia and glucocorticoid-induced apoptosis.

170. The method of claim 166, wherein the method results in one or more of the following:

(1) reduces one or more of fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;

(2) ameliorates one or more conditions or disorders that are characterized by elevations in one or more of the pathways or mechanisms involved in fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;

(3) increases fatty acid oxidation and ketogenesis;

(4) inhibits lipogenesis and/or isoprenaline-stimulated lipolysis;

(5) ameliorates one or more conditions or disorders that are characterized by elevations in one or both of lipogenesis and isoprenaline-stimulated lipolysis pathways, or that are exacerbated by the elevations in one or both of these pathways;

(6) decreases insulin secretion;

(7) ameliorates one or more a conditions or disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion;

(8) enhances glucose uptake in muscle cells;

(9) ameliorates one or more conditions or disorders that are characterized by decreased glucose uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle cells;

(10) reduces levels of cytoplasmic HuR, which in turn, in reduces concentrations and half-lives of target mRNA transcripts;

(11) ameliorates one or more conditions or disorders that are characterized decreased levels of HuR and its target transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target transcripts;

(12) provides protection against glucocorticoid-induced apoptosis;

(13) ameliorates one or more conditions or disorders that are characterized by increased glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced apoptosis;

(14) protects against cellular stresses resulting from ischemia;

(15) inhibits adipogenesis;

(16) ameliorates one or more conditions or disorders that are characterized by increased adipogenesis, or that are exacerbated by adipogenesis;

(17) protects neurons against metabolic and excitotoxic insults associated with the pathogenesis of a neurodegenerative condition;

(18) promotes astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism;

(19) increases insulin sensitivity of muscle glucose transport;

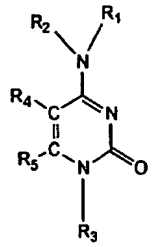
(20) protects against hepatic ischemia-reperfusion (I/R) injury associated with liver transplantation and hepatic resections;

(21) lowers blood glucose concentrations by decreasing hepatic glucose production and/or increasing glucose disposal in skeletal muscle; and

(22) ameliorates one or more conditions or disorders associated with insulin resistance syndrome through improving glucose tolerance, improving lipid profile or reducing systolic blood pressure.

171. The method of any one of claims 153-170, wherein said pharmaceutical composition is administered to said patient over a period of time of at least 28 days.

172. A pharmaceutical composition comprising a unit dosage of a cytosine derivative having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

173. The pharmaceutical composition of claim 172, wherein the unit dosage comprises one or more of: an acyl-cytidine and an acyl-cytosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

174. The pharmaceutical composition of claim 173, wherein the unit dosage comprises one or more of: a mono-acyl-cytidine and a mono-acyl-cytosine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

175. The pharmaceutical composition of claim 172, wherein the unit dosage comprises one or more of: an N6-acyl-cytosine and an N6-acyl-cytidine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

176. The pharmaceutical composition of claim 175, wherein the unit dosage comprises one or more of: N6-acetyl-cytosine and N6-acetyl-cytidine; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

177. The pharmaceutical composition of claim 172, wherein the unit dosage comprises one or more of: a naturally occurring cytosine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

178. The pharmaceutical composition of claim 172, wherein the unit dosage comprises one or more of: a non-naturally occurring cytosine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

179. The pharmaceutical composition of any one of claims 172-178, wherein the unit dosage comprises a cytosine derivative, and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof, in an amount sufficient to increase, following oral or parenteral administration of said unit dosage to a patient in need thereof, an intracellular level of activated AMPK and/or an intracellular level of activated Akt in one or more cell types and/or tissue types of said patient.

180. The pharmaceutical composition of claim 179, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least two-fold.

181. The pharmaceutical composition of claim 180, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least four-fold.

182. The pharmaceutical composition of claim 181, wherein the amount is sufficient to increase the intracellular level of activated AMPK and/or the intracellular level of activated Akt in one or more cell types and/or tissue types of said patient by at least ten-fold.

183. The pharmaceutical composition of any one of claims 179-182, wherein the one or more cell types and/or tissue types include one or more of: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.

184. The method of any one of claims 179-183, wherein the one or more cell types and/or tissue types include myocytes.

185. The pharmaceutical composition of any one of claims 172-184, wherein the pharmaceutical composition is in a form suitable for oral ingestion.

186. The pharmaceutical composition of claim 185, wherein the form suitable for oral ingestion is one or more of a pill, capsule, tablet, cachet or lozenge.

187. The pharmaceutical composition of any one of claims 172-184, wherein the pharmaceutical composition is in a form suitable parenteral injection.

188. The pharmaceutical composition of any one of claims 172-187, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

189. The pharmaceutical composition of any one of claims 172-188, wherein the pharmaceutical composition further comprises an additional therapeutic ingredient.

190. The pharmaceutical composition of claim 189, wherein the additional therapeutic ingredient is an anti-diabetic agent.

191. The pharmaceutical composition of claim 190, wherein the additional therapeutic ingredient is metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound, or a combination of any two or more thereof.

192. The pharmaceutical composition of claim 191, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.

193. The pharmaceutical composition of any one of claims 172-192, wherein one or more cytosine derivatives comprise, in total, at least at least 1%, by weight, of the pharmaceutical composition.

194. The pharmaceutical composition of claim 193, wherein one or more cytosine derivatives comprise, in total, at least 2%, 3%, 4%, 5%, 7.5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99%, by weight, of the pharmaceutical composition.

195. The pharmaceutical composition of any one of claims 172-194, wherein the pharmaceutical composition is a substantially pure pharmaceutical composition.

196. The pharmaceutical composition of any one of claims 172-195, wherein the pharmaceutical composition consists essentially of a cytosine derivative and a pharmaceutical carrier.

197. The pharmaceutical composition of any one of claims 172-196, comprising one or more cytosine derivatives purified from a plant or yeast extract.

198. The pharmaceutical composition of any one of claims 172-197, consisting essentially of:

(a) one or more of: a cytosine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier; and optionally

(c) one or more additional agents to treat diabetes.

199. The pharmaceutical composition of any one of claims 172-198, consisting essentially of:

(a) one or more of: a cytosine derivative; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof; and

(b) a pharmaceutically acceptable carrier.

200. A method for treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of the pharmaceutical composition of any one of claims 172-199.

201. A method of decreasing blood glucose level comprising the step of administering to a human or other animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 172-199.

202. A method of treating impaired glucose tolerance comprising the step of administering to a human or animal a therapeutically effective amount of the pharmaceutical composition of any one of claims 272-199.

203. The method according to any of claims 200, 201 and 202, wherein said pharmaceutical composition is administered in a dosage amount of from 0.001 mg/kg/day to 100 mg/kg/day.

204. The method according to claim 203, wherein the dosage amount is 0.1 mg/kg/day to 50 mg/kg/day.

205. A method of treating or preventing diabetes comprising the step of administering to a human or other animal an effective dosage of i) the pharmaceutical composition of any one of claims 272-199 in association with ii) one or more other agents chosen from: an agent or agents to treat diabetes, glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, glucosidase inhibitors and aldose reductase inhibitors.

206. The method of claim 205, wherein the agent or agents to treat diabetes include one of more of metformin, a sulfonylurea compound, or a thiazolidinedione (TZD) compound.

207. The method of claim 206, wherein the thiazolidinedione (TZD) compound is rosiglitazone or pioglitazone.

208. The method of claim 205, wherein the ingredients i) and ii) are simultaneously, separately, or sequentially administered.

209. A method for prophylaxis or treatment of a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity, said

method comprising the steps of: providing a patient suffering from or believed to be at risk of suffering from a disease or condition associated with hyperglycemia, insulin resistance, insulin resistance syndrome or obesity; and administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 272-199.

210. The method of claim 209, wherein said disease or condition is a vascular disease associated with metabolic abnormalities.

211. The method of claim 210, wherein said disease or condition is atherosclerotic vascular disease.

212. The method of claim 209, wherein said disease or condition is selected from the group consisting of blindness, retinopathy and nephropathy caused by diabetic microvascular disease.

213. A method for activating adenosine 5'-monophosphate-activated protein kinase (AMPK) and/or Akt in a patient in need thereof, the method comprising administering to said patient a therapeutically effective amount of the pharmaceutical composition of any one of claims 272-199.

214. The method of claim 213, wherein the patient suffers from obesity.

215. The method of claim 213, wherein the patient suffers from insulin resistance.

216. The method of claim 213, wherein the patient suffers from a condition or disorder selected from the group consisting of: non-insulin dependent (type 2) diabetes mellitus, high blood pressure, elevated levels of triglycerides, hyperinsulinemia, glucose intolerance, low levels of high density lipoprotein (HDL), ischemia, hypoxia and glucocorticoid-induced apoptosis.

217. The method of claim 213, wherein the method results in one or more of the following:

(1) reduces one or more of fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;

(2) ameliorates one or more conditions or disorders that are characterized by elevations in one or more of the pathways or mechanisms involved in fatty acid synthesis, sterol synthesis, triglyceride synthesis and fatty acid synthase gene expression;

(3) increases fatty acid oxidation and ketogenesis;

(4) inhibits lipogenesis and/or isoprenaline-stimulated lipolysis;

(5) ameliorates one or more conditions or disorders that are characterized by elevations in one or both of lipogenesis and isoprenaline-stimulated lipolysis pathways, or that are exacerbated by the elevations in one or both of these pathways;

(6) decreases insulin secretion;

(7) ameliorates one or more a conditions or disorders that are characterized by elevated insulin secretion, or that are exacerbated by insulin secretion;

(8) enhances glucose uptake in muscle cells;

(9) ameliorates one or more conditions or disorders that are characterized by decreased glucose uptake in muscle cells, or that are exacerbated by the effects of decreased glucose uptake in muscle cells;

(10) reduces levels of cytoplasmic HuR, which in turn, in reduces concentrations and half-lives of target mRNA transcripts;

(11) ameliorates one or more conditions or disorders that are characterized decreased levels of HuR and its target transcripts, or that are exacerbated by the effects of decreased levels of HuR and its target transcripts;

(12) provides protection against glucocorticoid-induced apoptosis;

(13) ameliorates one or more conditions or disorders that are characterized by increased glucocorticoid-induced apoptosis, or that are exacerbated by glucocorticoid-induced apoptosis;

(14) protects against cellular stresses resulting from ischemia;

(15) inhibits adipogenesis;

(16) ameliorates one or more conditions or disorders that are characterized by increased adipogenesis, or that are exacerbated by adipogenesis;

(17) protects neurons against metabolic and excitotoxic insults associated with the pathogenesis of a neurodegenerative condition;

(18) promotes astrocytes to produce ketone bodies as a substrate for neuronal oxidative metabolism;

(19) increases insulin sensitivity of muscle glucose transport;

(20) protects against hepatic ischemia-reperfusion (I/R) injury associated with liver transplantation and hepatic resections;

(21) lowers blood glucose concentrations by decreasing hepatic glucose production and/or increasing glucose disposal in skeletal muscle; and

(22) ameliorates one or more conditions or disorders associated with insulin resistance syndrome through improving glucose tolerance, improving lipid profile or reducing systolic blood pressure.

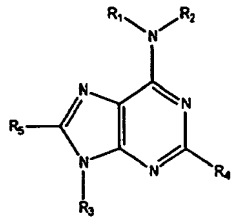
218. The method of any one of claims 200-217, wherein said pharmaceutical composition is administered to said patient over a period of time of at least 28 days.

219. A method for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), the method comprising:

1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK;

wherein the candidate compound is a cytokinin having the structure:



(I)

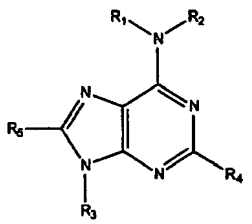
and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and

- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

220. The method of claim 219, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins of the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

221. A method for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), the method comprising:

1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK;

wherein the candidate compound is one or more cytokinins selected from:

N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium

salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

222. The method of claim 221,wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more cytokinins selected from: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate

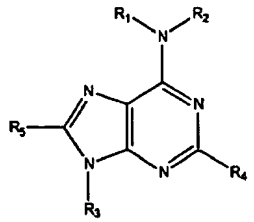
sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

223. A method for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), the method comprising:

1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK;

wherein the candidate compound is an adenine derivative having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

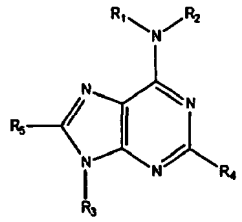
wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

224. The method of claim 223, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different adenine derivatives having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

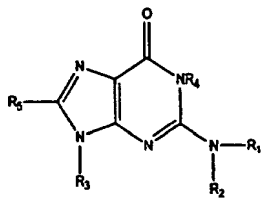
wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

225. A method for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), the method comprising:

1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK;

wherein the candidate compound is a guanine derivative having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

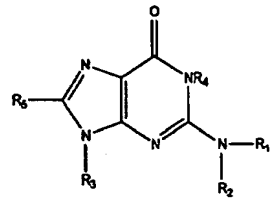
wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

226. The method of claim 225, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different guanine derivatives having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

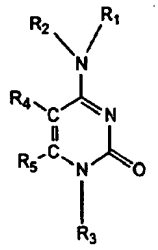
wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

227. A method for determining the degree to which a candidate compound activates adenosine monophosphate activated protein kinase (AMPK), the method comprising:

1) contacting cells or tissues expressing AMPK, or capable of expressing AMPK, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of AMPK activity to determine the degree to which the candidate compound activates AMPK;

wherein the candidate compound is a cytosine derivative having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

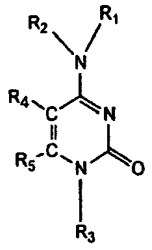
- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;

- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

228. The method of claim 227, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytosine derivatives having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;

- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

229. The method of any one of claims 219-228, wherein measuring the indicator of cellular AMPK activity comprises (i) measuring the phosphylation of AMPK and/or (ii) measuring the phosphylation of a protein that is phosphoralated by AMPK.

230. The method of claim 229, wherein measuring the indicator of cellular AMPK activity comprises measuring the phosphylation of AMPK.

231. The method of claim 230, wherein measuring the phosphylation of AMPK comprises measuring the phosphorylation of the threonine 172 residue of AMPK.

232. The method of any one of claims 219-228, wherein measuring the indicator of cellular AMPK activity comprises measuring the phosphylation of a protein that is phosphoralated by AMPK.

233. The method of claim 232, wherein the protein that is phosphoralated by AMPK is one of more proteins selected from the AMARA peptide and the SAMS peptide.

234. The method of claim 232, wherein the protein that is phosphoralated by AMPK is one of more proteins selected from the eNOS, nNOS and nNOSμ.

235. The method of any one of claims 229-234, wherein measuring the indicator of cellular AMPK activity further comprises measuring glucose uptake by cells and/or tissue.

236. The method of any one of claims 235, wherein the cells and/or tissues are selected from: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.

237. The method of any one of claims 235, wherein the cells are selected from the group consisting of: 3T3-LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells.

238. The method of any one of claims 219-228, wherein measuring the indicator of cellular AMPK activity comprises measuring the effect of the compound on glucose uptake glucose uptake by a cells and/or tissue.

239. The method of claim 238, wherein the cells and/or tissues are selected from: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.

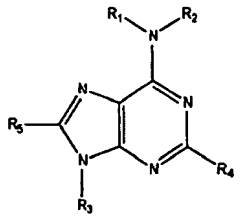
240. The method of claim 238, wherein the cells are selected from the group consisting of: 3T3-LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells.

241. A method for determining the degree to which a candidate compound activates Akt, the method comprising:

1) contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt;

wherein the candidate compound is a cytokinin having the structure:



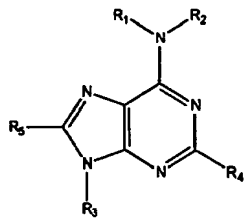
(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

242. The method of claim 241, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins having the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and

- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

243. A method for determining the degree to which a candidate compound activates Akt, the method comprising:

1) contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt;

wherein the candidate compound is one or more cytokinins selected from:

N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine;

2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

244. The method of claim 243, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more cytokinins selected from: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-

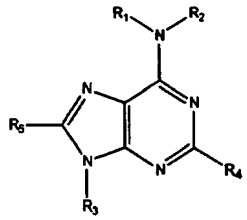
glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

245. A method for determining the degree to which a candidate compound activates Akt, the method comprising:

1) contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt;

wherein the candidate compound is an adenine derivative having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

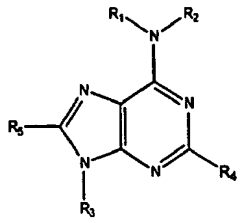
wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

246. The method of claim 245, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different adenine derivatives having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

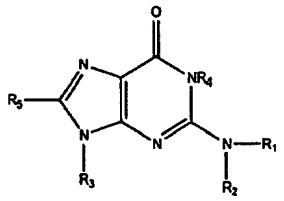
wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

247. A method for determining the degree to which a candidate compound activates Akt, the method comprising:

1) contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt;

wherein the candidate compound is a guanine derivative having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

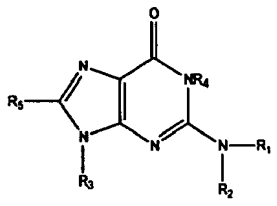
- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and

- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

248. The method of claim 247, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different guanine derivatives having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and

- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

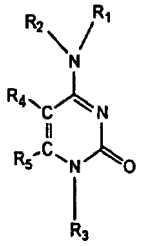
wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

249. A method for determining the degree to which a candidate compound activates Akt, the method comprising:

1) contacting cells or tissues expressing Akt, or capable of expressing Akt, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Akt activity to determine the degree to which the candidate compound activates Akt;

wherein the candidate compound is a cytosine derivative having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

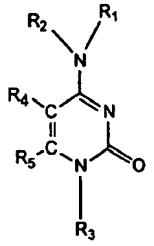
wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

250. The method of claim 249, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytosine derivatives having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

251. The method of any one of claims 241-250, wherein measuring the indicator of cellular Akt activity comprises (i) measuring the phosphylation of Akt and/or (ii) measuring the phosphylation of a protein that is phosphoralated by Akt.

252. The method of claim 251, wherein measuring the indicator of cellular Akt activity comprises measuring the phosphylation of Akt.

253. The method of claim 252, wherein measuring the phosphylation of Akt comprises measuring the phosphorylation of the serine 473 residue of Akt.

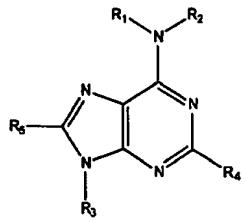
254. The method of claim 251, wherein measuring the indicator of cellular Akt activity comprises measuring the phosphylation of a protein that is phosphoralated by Akt.

255. A method for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising:

1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content;

wherein the candidate compound is a cytokinin having the structure:



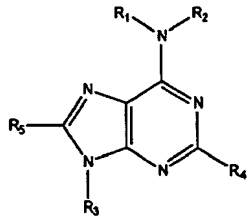
(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

256. The method of claim 255, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins having the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

257. A method for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising:

1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content;

wherein the candidate compound is one or more cytokinins selected from:

N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin

hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

258. The method of claim 257, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more cytokinins selected from: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-

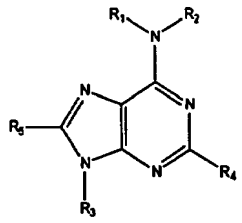
isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

259. A method for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising:

1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content;

wherein the candidate compound is an adenine derivative having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

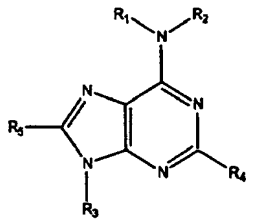
wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

260. The method of claim 259, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different adenine derivatives having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

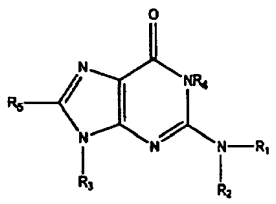
wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

261. A method for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising:

1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content;

wherein the candidate compound is a guanine derivative having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

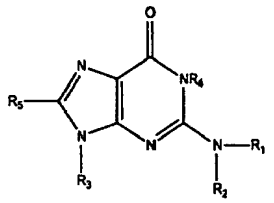
- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and

- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

262. The method of claim 261, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different guanine derivatives having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and

- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

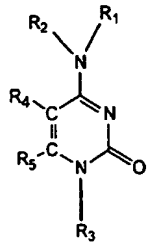
wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

263. A method for determining the degree to which a candidate compound increases Glut-4 content of a cell, the method comprising:

1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Glut-4 content to determine the degree to which the candidate compound increases Glut-4 content;

wherein the candidate compound is a cytosine derivative having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

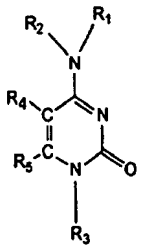
wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

264. The method of claim 263, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytosine derivatives having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

265. The method of any one of claims 255-264, wherein measuring the indicator of Glut-4 content comprises (i) measuring Glut-4 content of the cells and/or tissue and/or (ii) measuring glucose uptake glucose uptake by the cells and/or tissue.

266. The method of claim 265, wherein measuring the indicator of Glut-4 content comprises measuring Glut-4 content of the cells and/or tissue.

267. The method of claim 265, wherein measuring the indicator of Glut-4 content comprises measuring total Glut-4 content of the cells and/or tissue.

268. The method of claim 265, wherein measuring the indicator of Glut-4 content comprises measuring glucose uptake glucose uptake by the cells and/or tissue.

269. The method of any one of claims 255-268, wherein the cells and/or tissues are selected from: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.

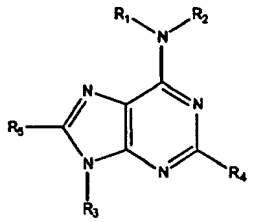
270. The method of any one of claims 255-268, wherein the cells are selected from the group consisting of: 3T3-LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells.

271. A method for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising:

1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;

wherein the candidate compound is a cytokinin having the structure:



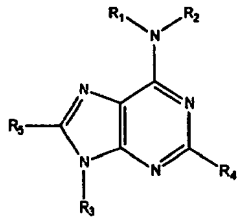
(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

272. The method of claim 271, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytokinins having the structure:



(I)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 is H or alkyl, lower alkyl, alkenyl, or acyl;
- R_2 is alkyl, lower alkyl or alkenyl;
- R_3 is hydrogen, alkyl, lower alkyl or saccharide; and
- R_4 and R_5 are the same or different and are individually hydrogen, alkyl, lower alkyl alkenyl or alkynyl.

273. A method for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising:

1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;

wherein the candidate compound is one or more cytokinins selected from:

N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin;

trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

274. The method of claim 273, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more cytokinins selected from: N6 – benzyladenine; N6 – benzyladenine hydrochloride; N6 – benzyladenosine; N6-benzyladenine-3-glucoside; N6-benzyladenine-7-glucoside; N6-benzyladenine-9-glucoside; N6-benzyl-9-(2-tetrahydropyranyl)adenine; N6 – benzyladenosine-5'-monophosphate sodium salt; N6-gamma, gamma-dimethyl-allyl-aminopurine; dihydro-zeatin; dihydrozeatin hydrochloride; dihydrozeatin riboside; dihydrozeatin-7-β-D-glucoside; dihydrozeatin-9-β-D-glucoside; dihydrozeatin-O-glucoside; dihydrozeatin-O-glucoside riboside; dihydrozeatin riboside-5'-monophosphate sodium salt; dihydrozeatin-O-acetyl; N6-isopentenyladenine; N6-isopentenyladenosine; N6-isopentenyladenine hydrochloride; N6-isopentenyladenosine-5'-monophosphate sodium salt; N6-isopentenyladenine-7-glucoside; N6-isopentenyladenine-9-glucoside; 2-methylthio-N6-isopentenyladenosine; 2-methylthio-N6-

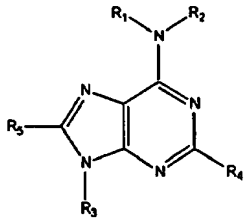
isopentenyladenine; 2-thio-N6-isopentenyladenine; 2-benzylthio-N6-isopentenyladenine; 2-isopentenylamine hydrochloride; kinetin; kinetin hydrochloride; kinetin riboside; kinetin-9-glucoside; kinetin riboside-5'-monophosphate sodium salt; meta-topolin; meta-topolin riboside; meta-topolin-9-glucoside; ortho-topolin; ortho-topolin riboside; ortho-topolin-9-glucoside; trans-zeatin; trans-zeatin riboside; cis-zeatin; cis-zeatin riboside; trans-zeatin hydrochloride; trans-zeatin-7-glucoside; trans-zeatin-9-glucoside; trans-zeatin-O-glucoside; trans-zeatin-O-glucoside riboside; trans-zeatin riboside-5'-monophosphate sodium salt; trans-zeatin-O-acetyl; 2-chloro-trans-zeatin; 2-methylthio-trans-zeatin; and 2-methylthio-trans-zeatin riboside; and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof.

275. A method for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising:

1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;

wherein the candidate compound is an adenine derivative having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

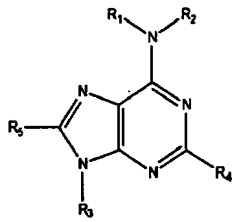
wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

276. The method of claim 275, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different adenine derivatives having the structure:



(II)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

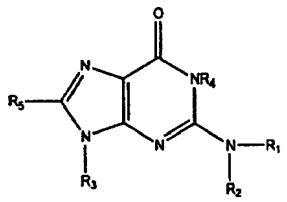
wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

277. A method for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising:

1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;

wherein the candidate compound is a guanine derivative having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

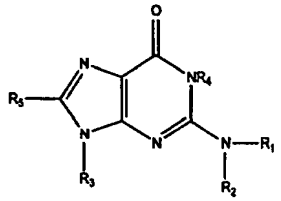
wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

278. The method of claim 277, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different guanine derivatives having the structure:



(III)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;
- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

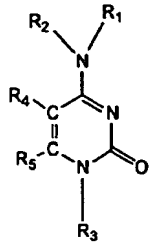
wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

279. A method for determining the degree to which a candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell, the method comprising:

1) contacting cells or tissues expressing Glut-4, or capable of expressing Glut-4, or cellular extracts therefrom, with the candidate compound; and

2) measuring an indicator of Glut-4 translocation to determine the degree to which the candidate compound enhances translocation of Glut-4 from an intracellular location to the plasma membrane of a cell;

wherein the candidate compound is a cytosine derivative having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

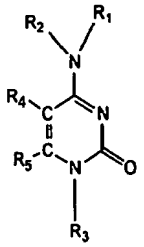
- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;

- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

280. The method of claim 279, wherein the candidate compound is selected from a group of candidate compounds, the group of candidate compounds comprising two or more different cytosine derivatives having the structure:



(IV)

and/or a racemate, enantiomer, tautomer, solvate, hydrate, pro-drug, polymorph and/or pharmaceutically acceptable salt thereof,

wherein:

- R_1 and R_2 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, heteroacyl, aryl, aralkyl or heterocyclyl;

- R_3 is hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, heterocyclyl, or saccharide,; and
- R_4 and R_5 are the same or different and are hydrogen, alkyl, lower alkyl, alkenyl, acyl, aryl, aralkyl, heteroacyl, or heterocyclyl;

wherein at least one of R_1, R_2, R_3, R_4, and R_5 is not hydrogen; and

wherein at least one of R_1, R_2, R_4, and R_5 is not hydrogen when R_3 is ribosyl, deoxyribosyl or 5'phospho-ribosyl or 5'phospho-deoxyribosyl.

281. The method of any one of claims 271-280, wherein measuring the indicator of Glut-4 translocation in the cells and/or tissue comprises (i) measuring plasma membrane Glut-4 content of the cells and/or tissue and/or (ii) measuring glucose uptake glucose uptake by the cells and/or tissue.

282. The method of claim 281, wherein measuring the indicator of Glut-4 translocation in the cell comprises measuring plasma membrane Glut-4 content of the cells and/or tissue.

283. The method of claim 283, measuring the indicator of Glut-4 translocation in the cells and/or tissue comprises measuring glucose uptake glucose uptake by the cells and/or tissue.

284. The method of any one of claims 271-283, wherein the cells and/or tissues are selected from: myocytes, fibroblasts, skeletal muscle cells, skeletal muscle tissue, liver cells, liver tissue, pancreatic cells, pancreatic tissue, adipocytes and adipose tissue.

285. The method of any one of claims 271-283, wherein the cells are selected from the group consisting of: 3T3-LI cells, Chinese Hamster Ovary cells, C2C12 cells and L6 cells.

ABSTRACT

Compounds and compositions are disclosed that modulate one or more of various metabolic activities. Among the disclosed compounds and compositions are those that potently activate AMPK and/or Akt. The use of such activators, as well as compositions comprising such activators, to increase intracellular levels of activated AMPK and/or activated Akt to result in one of a number of beneficial effects in an organism is also disclosed. Compounds and compositions having blood glucose lowering activity and/or lipid lowering activity are disclosed as are related methods using them. An aspect of the present invention is particularly concerned with an anti-diabetic agent and with an anti-diabetic composition containing the anti-diabetic agent. Another aspect of the invention is particularly concerned with methods relating to treating insulin resistance and/or diabetes, including type II diabetes. Also disclosed are screening methods for screening purine derivatives and/or pyrimidine derivatives to identify compounds having an activity to modulate one or more of various metabolic activities and/or for use as an anti-diabetic agent. The disclosed screening methods include measuring the ability of a purine derivative and/or a pyrimidine derivative to increase intracellular levels of activated AMPK and/or activated Akt.

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